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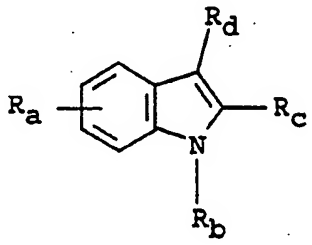
Title: SUBSTITUTED INDOLES WITH A THROMBIN-INHIBITING EFFECT

Abstract:

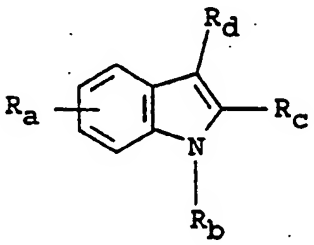


, (I)

The invention relates to new substituted indoles of general formula (I) in which R_a to R_d are defined as in claim 1. The tautomers, stereoisomers, mixtures and salts of R_a to R_d have valuable properties. The compounds of general formula (I) in which R_b or R_d contains a cyanophenyl group are valuable intermediate products in the production of the remaining compounds of general formula (I), and the compounds of general formula (I) in which R_b or R_d contains an R_1NH-C(=NH)-phenyl group in addition to the tautomers and stereoisomers thereof have valuable pharmacological properties, especially an antithrombotic effect, a thrombin time-extending effect and a fibrinogen-receptor antagonistic effect.

SUBSTITUTED INDOLES WITH A THROMBIN-INHIBITING EFFECT

The object of this invention is new substituted indoles of the general formula



, (I)

their tautomers, stereoisomers, mixtures and salts, and in particular their physiologically compatible salts with inorganic or organic acids or bases, which have valuable properties.

The compounds of the above general formula I, in which R_b or R_d contains a cyanophenyl group, are valuable intermediate products for producing the remaining compounds of general formula I, and the compounds of the above general formula I in which R_b or R_d contains an R_1NH-C(=NH)-phenyl group, as well as their tautomers and stereoisomers, have valuable pharmacological properties, in particular an antithrombotic effect which is due to a thrombin-inhibiting effect.

The object of this application is therefore the new compounds of the above general formula I, as well as their production, the drugs containing the pharmacologically active compounds, and their use.

In the above general formula,

R_a means a fluorine, chlorine or bromine atom, a carboxy, R_3R_4N-CO, R_3R_4N-SO_2 or R_4R_5N group or a group convertible in vivo into a carboxy group, in which

R_3 is a hydrogen atom, a C_{1-6}-alkyl, C_{3-7}-cycloalkyl, C_{3-7}-cycloalkyl-C_{1-3}-alkyl or phenyl-C_{1-3}-alkyl group,

an n-C_{2-3}-alkyl group which is substituted in the 2 or 3 position by a C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group,

a phenyl or naphthyl group optionally substituted by a trifluoromethyl group,

a phenyl or naphthyl group monosubstituted or disubstituted by a fluorine, chlorine or bromine atom or by a C_{1-3}-alkyl, C_{1-3}-alkoxy, carboxy-C_{1-3}-alkoxy or carboxy group, the substituents being able to be the same or different,

a phenyl group substituted by three C_{1-3}-alkyl groups or by one amino group and two chlorine or bromine atoms,

a furanyl, thienyl, oxazolyl, thiazolyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl group optionally substituted in the carbon network by a C_{1-3}-alkyl group, to which furanyl, thienyl, oxazolyl, thiazolyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl group a phenyl ring can also be condensed via two carbon atoms in the o position, or one of the aforementioned nitrogen-containing rings in which a nitrogen atom is quarternized by a C_{1-3}-alkylbromide or C_{1-3}-alkyliodide,

R_4 is a hydrogen atom or a C_{1-3}-alkyl group substituted by a carboxy, carboxy-C_{1-3}-alkylamino, di-(carboxy-C_{1-3}-alkyl)-amino, carboxy-C_{1-3}-alkylaminocarbonyl or di-(carboxy-C_{1-3}-alkyl)-aminocarbonyl group, the carboxy groups mentioned above in the definition of the radicals R_3 and R_4 being able to be replaced by a group that is convertible *in vivo* into a carboxy group, or

R_3 and R_4 together with the intervening nitrogen atom are a pyrrolidino, piperidino or hexamethylene imino group,

R_5 is a phenylaminocarbonyl, naphthylaminocarbonyl, R_6CO or R_6SO_2 group in which R_6 has in each case the meanings given above for R_3 except for the hydrogen atom, or

R_4 and R_5 together with the intervening nitrogen atom are an imidazolidine-2,4-dione group substituted by a phenyl group in the 3 position,

one of the radicals R_b or R_d means a C_{1-3}-alkyl group that can be substituted by a carboxy group or a group convertible *in vivo* into a carboxy group, and the other radical of the radicals R_b or R_d means an R_2-A group, in which

A is an n-C_{1-3}-alkylene group which can be substituted by a C_{1-3}-alkyl group optionally substituted by a carboxy group or by a group convertible *in vivo* into a carboxy group, an indole-ring-linked methylene group of the n-C_{1-3}-alkylene group also being able to be replaced by a carbonyl group, or a -CONH-, -CH_2CONH-, -CH_2CH_2CONH-, -CONHCH_2-, -CONCH_2CH_2-, -$COCH_2O$- or -$COCH_2CH_2O$- group, the oxygen atom of the -$COCH_2O$- and -$COCH_2CH_2O$- group being linked in each case to radical R_2, and

R_2 is a phenyl group substituted by the R_1NH-C(=NH) group, in which phenyl group R_1 means a hydrogen atom or an *in vivo* cleavable radical,

and R_c means a hydrogen atom or a C_{1-3}-alkyl group.

A group convertible *in vivo* into a carboxy group is understood to mean, for example, a hydroxymethyl group, a carboxy group esterified with an alcohol, in which group the alcoholic part, preferably a C_{1-6}-alkanol, a phenyl-C_{1-3}-alkanol, a C_{3-9}-cycloalkanol, whereby a C_{5-8}-cycloalkanol can also be substituted by one or two C_{1-3}-alkyl groups, a C_{5-8}-cycloalkanol, in which a methylene group in the 3 or

4 position is replaced by an oxygen atom or by an imino group optionally substituted by a C_{1-3}-alkyl, phenyl-C_{1-3}-alkyl, phenyl-C_{1-3}-alkoxycarbonyl or C_{2-6}-alkanoyl group, and the cycloalkanol part can also be substituted by one ot two C_{1-3}-alkyl groups, a C_{4-7}-cycloalkenol, a C_{3-5}-alkenol, a phenyl-C_{3-5}-alkenol, a C_{3-5}-alkinol or phenyl-C_{3-5}-alkinol with the condition that no bond to the oxygen atom comes from a carbon atom bearing a double or triple bond, a C_{3-8}-cycloalkyl-C_{1-3}-alkanol, a bicycloalkanol with a total of 8 to 10 carbon atoms which can also be substituted by one or two C_{1-3}-alkyl groups, a 1,3-dihydro-3-oxo-1-isobenzofuranol or an alcohol of the formula

$$R_7\text{-CO-O-}(R_8CR_9)\text{-OH},$$

in which
R_7 is a C_{1-8}-alkyl, C_{5-7}-cycloalkyl, phenyl or phenyl-C_{1-3}-alkyl group,

R_8 is a hydrogen atom, a C_{1-3}-alkyl, C_{5-7}-cycloalkyl or phenyl group and

R_9 is a hydrogen atom or a C_{1-3}-alkyl group,

or a radical cleavable *in vivo* from an imino or amino group is understood to mean, for example, a hydroxy group, an acyl group such as the benzoyl or pyridinoyl group or a C_{1-16}-alkanoyl group such as the formyl, acetyl, propionyl, butanoyl, pentanoyl or hexanoyl group, an allyloxycarbonyl group, a C_{1-16}-alkoxy-carbonyl group such as the methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, tert. butoxycarbonyl, pentoxycarbonyl, hexoxycarbonyl, octyloxycarbonyl, nonyloxycarbonyl, decyloxycarbonyl, undecyloxycarbonyl, dodecyloxycarbonyl or hexadecyloxycarbonyl group, a phenyl-C_{1-16}-alkoxycarbonyl group such as the benzyloxycarbonyl, phenylethoxycarbonyl or phenylpropoxycarbonyl group, a C_{1-3}-alkylsulfonyl-C_{2-4}-alkoxycarbonyl, C_{1-3}-alkoxy-C_{2-4}-alkoxy-C_{2-4}-alkoxycarbonyl or $R_7CO\text{-O-}(R_8CR_9)$-O-CO group in which R_7 through R_9 are as defined above.

The saturated alkyl and alkoxy parts containing more than 2 carbon atoms mentioned above in the definition, as well as alkanoyl parts and unsaturated alkyl parts containing more than 3 carbon atoms, also include their ramified isomers such as, for example, the isopropyl, tert. butyl, isobutyl group etc.

Preferred compounds of the above general formula I are those in which

R_a means a fluorine, chlorine or bromine atom, a carboxy, C_{1-3}-alkoxycarbonyl, $R_3R_4N\text{-CO}$, $R_3R_4N\text{-SO}_2$ or R_4R_5N group, in which

R_3 is a hydrogen atom, a C_{1-6}-alkyl, C_{3-7}-cycloalkyl, C_{3-7}-cycloalkyl-C_{1-3}-alkyl or phenyl-C_{1-3}-alkyl group, an n-C_{2-3}-alkyl group, which is substituted in the 2 or 3 position by a C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group,

a phenyl or naphthyl group,

a phenyl or naphthyl group monosubstituted or disubstituted by a fluorine, chlorine or bromine atom, by a C_{1-3}-alkyl, C_{1-3}-alkoxy, carboxy-C_{1-3}-alkoxy,

C_{1-3}-alkoxycarbonyl-C_{1-3}-alkoxy, carboxy, C_{1-3}-alkoxycarbonyl group, the substituents being able to be the same or different,

a phenyl group substituted by three C_{1-3}-alkyl groups or by one amino group and two chlorine or bromine atoms,

a furanyl, thienyl, oxazolyl, thiazolyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl group optionally substituted in the carbon network by a C_{1-3}-alkyl group, to which furanyl, thienyl, oxazolyl, thiazolyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl group a phenyl ring can also be condensed via two carbon atoms in the o position, or one of the aforementioned nitrogen-containing rings in which a nitrogen atom is quarternized by a C_{1-3}-alkylbromide or C_{1-3}-alkyliodide,

R_4 is a hydrogen atom or a C_{1-3}-alkyl group substituted by a carboxy, carboxy-C_{1-3}-alkylamino, di-(carboxy-C_{1-3}-alkyl)-amino, C_{1-3}-alkoxycarbonyl, C_{1-3}-alkoxycarbonyl-C_{1-3}-alkylamino, di-(C_{1-3}-alkoxycarbonyl-C_{1-3}-alkyl)-amino, carboxy-C_{1-3}-alkylaminocarbonyl, di-(carboxy-C_{1-3}-alkyl)-aminocarbonyl, C_{1-3}-alkoxycarbonyl-C_{1-3}-alkylaminocarbonyl or di-(C_{1-3}-alkoxycarbonyl-C_{1-3}-alkyl)-aminocarbonyl group,

R_3 and R_4 together with the intervening nitrogen atom are a pyrrolidino, piperidino or hexamethylene imino group,

R_5 is a phenylaminocarbonyl, naphthylaminocarbonyl, R_6CO or R_6SO_2 group in which R_6 has in each case the meanings given above for R_3 except for the hydrogen atom, or

R_4 and R_5 together with the intervening nitrogen atom are an imidazolidine-2,4-dione group substituted by a phenyl group in the 3 position,

one of the radicals R_b or R_d means a C_{1-3}-alkyl group that can be substituted by a carboxy or C_{1-3}-alkoxycarbonyl group, and the other radical of the radicals R_b or R_d means an R_2-A group, in which

A is an n-C_{1-3}-alkylene group which can be substituted by a C_{1-3}-alkyl group optionally substituted by a carboxy or C_{1-3}-alkoxycarbonyl group, an indole-ring-linked methylene group of the n-C_{1-3}-alkylene group also being able to be replaced by a carbonyl group, or a -CONH-, -CH_2CONH-, -CH_2CH_2CONH-, -CONHCH_2-, -CONCH_2CH_2-, -$COCH_2O$- or -$COCH_2CH_2O$- group, the oxygen atom of the -$COCH_2O$- and -$COCH_2CH_2O$- group being linked in each case to radical R_2, and

R_2 is a phenyl group substituted by the R_1NH-C(=NH) group, in which phenyl group

R_1 means a hydrogen atom or an *in vivo* cleavable radical,

and R_c means a hydrogen atom or a C_{1-3}-alkyl group, and tautomers, stereosiomers and salts thereof.

Especially preferred compounds of the above general formula I are those in which

R_a in the 5 or 6 position means an R_3R_4N-CO, R_3R_4N-SO_2 or R_4R_5N group, in which

R_3 is a hydrogen atom, a C_{1-6}-alkyl, C_{3-7}-cycloalkyl, C_{3-7}-cycloalkyl-C_{1-3}-alkyl or phenyl-C_{1-3}-alkyl group,

a phenyl or naphthyl group monosubstituted or disubstituted by a fluorine, chlorine or bromine atom, by a C_{1-3}-alkyl, C_{1-3}-alkoxy, carboxy-C_{1-3}-alkoxy, C_{1-3}-alkoxycarbonyl-C_{1-3}-alkoxy, carboxy, C_{1-3}-alkoxycarbonyl group, the substituents being able to be the same or different,

a phenyl group substituted by three C_{1-3}-alkyl groups or by one amino group and two chlorine or bromine atoms,

a furanyl, thienyl, oxazolyl, thiazolyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl group optionally substituted in the carbon network by a C_{1-3}-alkyl group, to which furanyl, thienyl, oxazolyl, thiazolyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl group a phenyl ring can also be condensed via two carbon atoms in the o position, or one of the aforementioned nitrogen-containing rings in which a nitrogen atom is quarternized by a C_{1-3}-alkylbromide or C_{1-3}-alkyliodide,

R_4 is a hydrogen atom or a C_{1-3}-alkyl group substituted by a carboxy, C_{1-3}-alkyloxycarbonyl, carboxy-C_{1-3}-alkylaminocarbonyl, di-(carboxy-C_{1-3}-alkyl)-aminocarbonyl, C_{1-3}-alkoxycarbonyl-C_{1-3}-alkylaminocarbonyl or di-(C_{1-3}-alkoxycarbonyl-C_{1-3}-alkyl)-aminocarbonyl group,

R_3 and R_4 together with the intervening nitrogen atom are a pyrrolidino, piperidino or hexamethylene imino group,

R_5 is an R_6CO or R_6SO_2 group in which R_6 has in each case the meanings given above for R_3 except for the hydrogen atom,

one of the radicals R_b or R_d means a C_{1-3}-alkyl group that can be substituted by a carboxy or C_{1-3}-alkoxycarbonyl group, and the other radical of the radicals R_b or R_d means an R_2-A group, in which

A is an n-C_{1-3}-alkylene group which can be substituted by a C_{1-3}-alkyl group optionally substituted by a carboxy or C_{1-3}-alkoxycarbonyl group, an indole-ring-linked methylene group of the n-C_{1-3}-alkylene group also being able to be replaced by a carbonyl group, or a -CONH-, -CH_2CONH-, -CH_2CH_2CONH-, -CONHCH_2-, -CONCH_2CH_2-, -$COCH_2$O- or -$COCH_2CH_2$O- group, the oxygen atom of the -$COCH_2$O- and -$COCH_2CH_2$O- group being linked in each case to radical R_2, and

R_2 is a phenyl group substituted by the R_1NH-C(=NH) group, in which phenyl group

R_1 means a hydrogen atom or an *in vivo* cleavable radical,

and R_c means a hydrogen atom, and tautomers, stereosiomers and salts thereof.

The most especially preferred compounds of the above general formula I are those in which

R_a in the 5 position means an R_3R_4N-CO, R_3R_4N-SO_2 or R_4R_5N group, in which

R_3 is a thienyl, thiazolyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl group optionally substituted in the carbon network by methyl group, to which thienyl, thiazolyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl group a phenyl ring can also be condensed via two carbon atoms in the o position,

R_4 is a C_{1-3}-alkyl group substituted by a carboxy, C_{1-3}-alkoxycarbonyl, carboxy-C_{1-3}-alkylaminocarbonyl or C_{1-3}-alkoxycarbonyl-C_{1-3}-alkylaminocarbonyl group,

R_5 is an R_6CO or R_6SO_2 group in which R_6 has in each case the meanings given above for R_3 except for the hydrogen atom,

R_b means a C_{1-3}-alkyl group and

R_d means an R_2A group, in which

A is a -$COCH_2$ or -$COCH_2CH_2$ group and

R_2 is a phenyl group substituted by the R_1NH-C(=NH) group, in which phenyl group

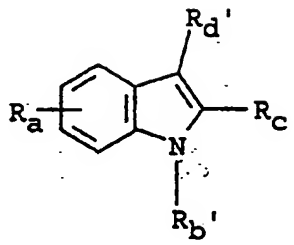
R_1 is a hydrogen atom or a C_{1-3}-alkoxycarbonyl group,

and R_c means a hydrogen atom, and tautomers, stereosiomers and salts thereof.

The new compounds can be produced in accordance with known procedures, for example, the following procedures:

a. To produce a compound of general formula I, in which R_2 is a phenyl group substituted by the NH_2-C(=NH) group:

Reaction of a compound optionally formed in the reaction mixture of the general formula



, (II)

in which
R_a and R_c are as initially defined,
one of the radicals R_b' or R_d' is a C_{1-3}-alkyl group which can be substituted by a C_{1-3}-alkoxycarbonyl group, and the other radical of radicals R_b' or R_d' is an R_2'-A group in which

A is as defined initially and
R_2' is a phenyl group substituted by a Z_1-C(=NH) group, in which phenyl group

Z_1 is an alkoxy or aralkoxy group such as the methoxy, ethoxy, n-propoxy, isopropoxy or benzyloxy group or an alkylthio or aralkylthio group such as the methylthio, ethylthio, n-propylthio or benzylthio group,

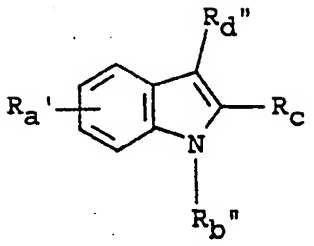
with ammonia or its salts.

The reaction is performed in a solvent such as methanol, ethanol, n-propanol, water, methanol/water, tetrahydrofuran or dioxane at temperatures between 0 and 150°C, preferably at temperatures between 0 and 80°C, with ammonia or with an acid addition salt such as, for example, ammonium carbonate or ammonium acetate.

A compound of general formula II is obtained, for example, by reacting *an appropriate* cyano compound with an appropriate alcohol such as methanol, ethanol, n-propanol, isopropanol or benzylalcohol in the presence of an acid such as hydrochloric acid or by reacting an appropriate amide with a trialkyloxonium salt such as triethyloxonium tetrafluoroborate in a solvent such as methylene chloride, tetrahydrofuran or dioxane at temperatures between 0 and 50°C, but preferably at 20°C, or by reacting an appropriate nitrile with hydrogen sulfide in a solvent such as pyridine or dimethylformamide and in the presence of a base such as triethylamine, followed by alkylation of the formed thioamide with an appropriate alkyl or aralkyl halide.

b. To produce a compound of general formula I, in which at least one of the radicals R_a, R_b and R_d contains a carboxy group and/or R_b or R_d contain an NH_2-C(=NH) group:

Conversion of a compound of the general formula



, (III)

in which
R_c is as initially defined,
R_a', R_b'' and R_d'' have the meanings initially given for R_a, R_b and R_d with the condition that at least one of the radicals R_a, R_b and R_d contains a group convertible into a carboxyl group by hydrolysis, treatment with an acid or base, thermolysis or hydrogenolysis and/or R_b or R_d contains a group convertible into an NH_2-C9=NH) group by hydrolysis, treatment with an acid or base, thermolysis or hydrogenolysis,

by means of hydrolysis, treatment with an acid or base, thermolysis or hydrogenolysis into a compound of general formula I, in which at least one of the radicals R_a, R_b and R_d contains a carboxy group and/or R_b or R_d contains an NH_2-C(=NH) group.

A group convertible into a carboxy group can be, for example, a carboxyl group protected by a protective radical such as its functional derivatives, e.g., its unsubstituted or substituted amides, esters, thioesters, trimethylesters, orthoesters or iminoesters, which are expediently converted into a carboxyl group by hydrolysis,

its esters with tertiary alcohols, e.g., tert. butylester, which are expediently converted into a carboxyl group by means of treatment with an acid or by thermolysis, and

its esters with aralkanols, e.g. benzylester, which are expediently converted into a carboxyl group by means of hydrogenolysis.

Hydrolysis is expediently performed either in the presence of an acid such as hydrochloric acid, sulfuric acid, phosphoric acid, acetic acid, trichloroacetic acid, trifluoroacetic acid or mixtures thereof, or in the presence of a base such as lithium hydroxide, sodium hydroxide or potassium hydroxide in a suitable solvent such as water, water/methanol, water/ethanol, water/isopropanol, methanol, ethanol, water/tetrahydrofuran or water/dioxane at temperatures between -10 and 120°C, e.g., at temperatures between room temperature and the boiling temperature of the reaction mixture.

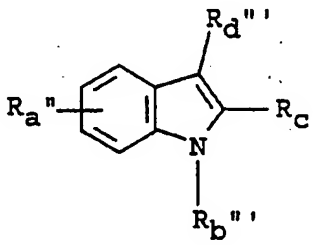
If a compound of formula III contains, for example, the tert. butyl or tert. butyloxy carbonyl group, these can be cleaved off by treatment with an acid such as trifluoroacetic acid, formic acid, p-toluene-sulfonic acid, sulfuric acid, hydrochloric acid, phosphoric acid or polyphosphoric acid optionally in an inert solvent such as methylene chloride, chloroform, benzene, toluene, diethylether,

tetrahydrofuran or dioxane preferably at temperatures between -10 and 120°C, e.g., at temperatures between 0 and 60°C, or also thermally optionally in an inert solvent such as methylene chloride, chloroform, benzene, toluene, tetrahydrofuran or dioxane and preferably in the presence of a catalytic amount of an acid such as p-toluene-sulfonic acid, sulfuric acid, phosphoric acid or polyphosphoric acid preferably at the boiling temperature of the solvent used, e.g., at temperatures between 40 and 120°C.

If a compound of formula III contains, for example, the benzyloxy or benzyloxycarbonyl group, these can also be cleaved off hydrogenolytically in the presence of a hydration catalyst such as palladium/carbon in a suitable solvent such as methanol, ethanol, ethanol/water, glacial acetic acid, acetic acid ethylester, dioxane or dimethylformamide preferably at temperatures between 0 and 50°, e.g., at room temperature, and at a hydrogen pressure of 1 to 5 bar.

c. To produce a compound of general formula I in which at least one of the radicals R_a, R_b and R_d contains an initially mentioned group convertible *in vivo* into a carboxy group:

Reaction of a compound of the general formula



, (IV)

in which
R_c is as initially defined,
R_a", R_b" and R_d" have the meanings initially given for R_a, R_b and R_d, with the condition that at least one of the radicals R_a, R_b and R_d contains a carboxy group or a group convertible by means of an alcohol into *an appropriate* ester group,

with an alcohol of the general formula

$$HO - R_{10} \quad , (V)$$

in which
R_{10} is the alkyl part of one of the initially mentioned *in vivo* cleavable radicals with the exception of the R_7-CO-O(R_8CR_9) group for a carboxyl group,

or with its formamide acetals

or with a compound of the general formula

$$Z_2 - R_{11} \quad , (VI)$$

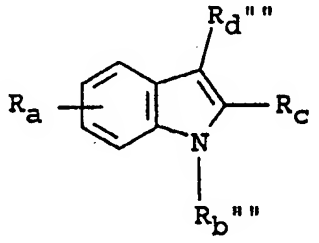
in which
R_{11} is the alkyl part of one of the initially mentioned in-vivo cleavable radicals for a carboxyl group and
Z_2 is a starting group such as a halogen atom, e.g., a chlorine or bromine atom.

The reaction with an alcohol of general formula V is expediently performed in a solvent or solvent mixture such as methylene chloride, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxane, but preferably in an alcohol of general formula V, optionally in the presence of an acid such as hydrochloric acid or in the presence of a dehydrating agent, e.g, in the presence of chloroformic acid isobutylester, thionyl chloride, trimethylchlorosilane, hydrochloric acid, sulfuric acid, methanosulfonic acid, p-toluene sulfonic acid, phosphor trichloride, phosphor pentoxide, N.N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide, N,N'-carbonyldiimidazole or N,N'-thionyldiimidazole, triphenylphosphine/carbon tetrachloride or triphenylphosphine/azodicarboxylic acid diethylester optionally in the presence of a base such as potassium carbonate, N-ethyl-diisopropylamine or N,N-dimethylamino pyridine expediently at temperatures between 0 and 150°C, preferably at temperatures between 0 and 80°C.

With a compound of general formula VI, the reaction is expediently performed in a solvent such as methylene chloride, tetrahydrofuran, dioxane, dimethylsulfoxide, dimethylformamide or acetone optionally in the presence of a reaction accelerant such as sodium or potassium iodide and preferably in the presence of a base such as sodium carbonate or potassium carbonate or in the presence of a tertiary organic base such as N-ethyldiisopropylamine or N-methyl-morpholine, which can also serve as solvents, or optionally in the presence of silver carbonate or silver oxide at temperatures between -30 and 100°C, but preferably at temperatures between -10 and 80°C.

d. To produce a compound of general formula I, in which R_2 is an in-vivo cleavable radical:

Reaction of a compound of the general formula



, (VII)

in which
R_a and R_c are as initially defined,
R_b" " and R_d" " have the meanings initially given for R_b and R_d, with the condition that R_2 is a phenyl group substituted by an NH_2-C(=NH) group,

with a compound of the general formula

$$Z_3 - R_{12} \quad , (VIII)$$

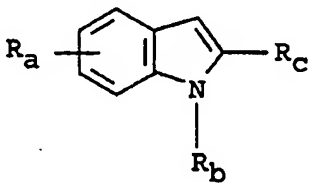
in which
R_{12} is one of the in-vivo cleavable radicals initially mentioned in the definition of the radical R_2 and
Z_3 means a nucleofugic starting group such as a halogen atom, e.g., a chlorine, bromine or iodine atom.

The reaction is performed preferably in a solvent such as methanol, ethanol, methylene chloride, tetrahydrofuran, toluene, dioxane, dimethylsulfoxide or dimethylformamide optionally in the presence of an inorganic or a tertiary organic base, preferably at temperatures between 20°C and the boiling temperature of the solvent used.

With a compound of general formula VIII, in which Z_3 is a nucleofugic starting group, the reaction is preferably performed in a solvent such as methylene chloride, acetonitrile, tetrahydrofuran, toluene, dimethylformamide or dimethylsulfoxide optionally in the presence of a base such as sodium hydride, potassium carbonate, potassium tert. butylate or N-ethyl-diisopropylamine at temperatures between 0 and 60°C.

e. To produce a compound of general formula I in which the R_2-A group is in the 3 position, R_2 is a cyanophenyl group and A is an n-C_{1-3}-alkylene group in which an indole-ring linked methylene group of the n-C_{1-3}-alkylene group is replaced by a carbonyl group, a -$COCH_2O$ or a -$COCH_2CH_2O$ group, the oxygen atom being linked to the radical R_2 in each case:

Reaction of a compound of general the formula



, (IX)

in which
R_a through R_c are as initially defined,

with a compound of the general formula

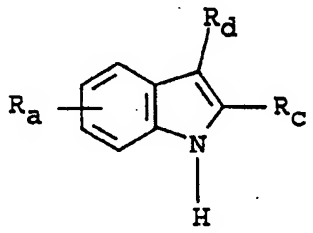
$$Z_4 - CO\text{-}A' - R_2' \quad , (X)$$

in which
R_2' means a cyanophenyl group,
A' means an n-C_{2-3}-alkylene group, a -CH_2O group or a -CH_2CH_2O group, the oxygen atom being linked to the radical R_2' in each case, and
Z_4 means a nucleofugic starting group such as a halogen atom, e.g., a chlorine, bromine or iodine atom.

The reaction is expediently performed in a solvent such as dichloromethane or dichloroethane in the presence of a Lewis acid such as aluminum trichloride at temperatures between 20 and 100°C, preferably at temperatures between 50 and 80°C.

f. To produce a compound of general formula I in which the R_2-A group is in the 1 position and A is an n-C_{1-3}-alkylene group in which an indole-ring linked methylene group of the n-C_{1-3}-alkylene group is replaced by a carbonyl group, a -$COCH_2O$ group or a -$COCH_2CH_2O$ group, the oxygen atom being linked to the radical R_2 in each case:

Reaction of a compound of general the formula



, (XI)

in which
R_a, R_c and R_d are as initially defined,

with a compound of the general formula

HO-CO-A'-R_2" , (XII)

in which
R_2" has the meanings initially given for R_2 with the condition that R_1 is as initially defined except for the hydrogen atom or is a protective radical for an amidino group and
A' is an n-C_{2-3}-alkylene group, a -CH_2O group or a -CH_2CH_2O group, the oxygen atom being linked to the radical R_2' in each case, or with reactive derivatives thereof and optionally followed by cleavage of any protective radical used.

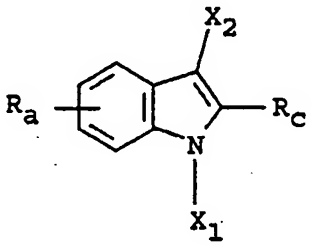
The reaction of an acid of general formula XII is optionally performed in a solvent or mixture of solvents such as methylene chloride, dimethylformamide, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxane, optionally in the presence of an acid such as hydrochloric acid or in the presence of a dehydrating agent, e.g, in the presence of chloroformic acid isobutylester, orthocarboxylic acid tetraethylester, orthoacetic acid trimethylester, 2,2-dimethoxypropane, tetramethoxysilane, thionyl chloride, trimethylchlorosilane, phosphor trichloride, phosphor pentoxide, N.N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide, N,N'-dicyclohexylcarbodiimide/1--hydroxy-benzotriazole, 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium-tetrafluoroborate, 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium-tetrafluoroborate / 1-hydroxy-benzotriazole, N,N'-carbonyldiimidazole or triphenylphosphine/carbon tetrachloride, and optionally

with the addition of a base such as pyridine, 4-dimethylamino pyridine, N-methyl-morpholine or triethylamine expediently at temperatures between 0 and 150°C, preferably at temperatures between 0 and 80°C.

The reaction of *an appropriate* reactive compound of general formula XII such as its esters, imidazolides or halides is preferably performed in a solvent such as methylene chloride or ether and preferably in the presence of a tertiary organic base such as triethylamine, N-ethyl-diisopropylamine or N-methyl-morpholine at temperatures between 0 and 150°C, preferably at temperatures between 50 and 100°C.

g. To produce a compound of general formula I in which the R_2-A group is in the 1 or 3 position, R_2 is a cyanophenyl group and A is a -CONH group, a -CH_2CONH group, a -CH_2CH_2CONH group, a -CONHCH_2 group or a -CONHCH_2CH2 group:

Reaction of a compound of the general formula



, (XIII)

in which
R_a and R_c are as initially defined,
one of the radicals X_1 or X_2 is a C_{1-3}-alkyl group that can be substituted by a C_{1-3}-alkoxycarbonyl group, and the other radical X_1 or X_2 is an HOOC-$(CH_2)_n$ group in which

n is the number 0, 1 or 2,

with a compound of the general formula

$$H_2N\text{-}(CH_2)_m\text{-}R_2' \quad , (XIV)$$

in which
R_2' means a cyanophenyl group and
m is the number 0, 1 or 2,

or with i reactive derivatives thereof.

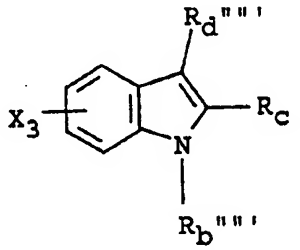
The reaction of an acid of general formula XIII is optionally performed in a solvent or mixture of solvents such as methylene chloride, dimethylformamide, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxane, optionally in the presence of a dehydrating agent, e.g, in the presence of chloroformic acid isobutylester, orthocarboxylic acid tetraethylester, orthoacetic acid trimethylester, 2,2-dimethoxypropane, tetramethoxysilane, thionyl chloride, trimethylchlorosilane, phosphor trichloride, phosphor pentoxide, N.N'-

dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide, N,N'-dicyclohexylcarbodiimide/1-hydroxy-benzotriazole, 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium-tetrafluoroborate, 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium-tetrafluoroborate / 1-hydroxy-benzotriazole, N,N'-carbonyldiimidazole or triphenylphosphine/carbon tetrachloride, and optionally with the addition of a base such as pyridine, 4-dimethylamino pyridine, N-methyl-morpholine or triethylamine expediently at temperatures between 0 and 150°C, preferably at temperatures between 0 and 100°C.

The reaction of *an appropriate* reactive compound of general formula XIII such as esters, imidazolides or halides thereof is preferably performed in a solvent such as methylene chloride or ether and preferably in the presence of a tertiary organic base such as triethylamine, N-ethyl-diisopropylamine or N-methyl-morpholine at temperatures between 0 and 150°C, preferably at temperatures between 50 and 100°C.

h. To produce a compound of general formula I in which R_a is a C_{1-3}-alkoxycarbonyl group, an R_3R_4N-CO group, an R_3R_4N-SO_2 group or an R_4R_5N group and R_2 is a cyanophenyl group:

Reaction of a compound of the general formula



, (XV)

with a compound of the general formula

$$X_4\text{-}Y \quad , (XVI)$$

in which
R_c is as initially defined,
one of the radicals R_b" " ' or R_d" " ' is a C_{1-3}-alkyl group that can be substituted by a C_{1-3}-alkoxycarbonyl group, and the other of the radicals R_b" " ' or R_d" " ' is an R_2'-A group in which

A is as initially defined and R_2' is a cyanophenyl group,

X_3 is an HO-CO or HO-SO_2 group, X_4 is a hydrogen atom and Y is a C_{1-3}-alkyl group or an R_3R_4N group or

X_3 is an R_4NH group, X_4 is a phenylamino, naphthylamino or R_6 group, with R_3 and R_4 being as initially defined, and R_6 having the meanings initially given for R_3 except for the hydrogen atom, and

Y is an HO-CO or HO-SO_2 group, with the hydroxy group of the HO-CO or HO-SO_2 group together with the hydrogen atom of an amino group of radical X_4 also being able to be another carbon-nitrogen bond,

or with reactive derivatives thereof.

The reaction of *an appropriate* acid is optionally performed in a solvent or mixture of solvents such as methylene chloride, dimethylformamide, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxane, optionally in the presence of a dehydrating agent, e.g, in the presence of chloroformic acid isobutylester, orthocarboxylic acid tetraethylester, orthoacetic acid trimethylester, 2,2-dimethoxypropane, tetramethoxysilane, thionyl chloride, trimethylchlorosilane, phosphor trichloride, phosphor pentoxide, N.N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide, N,N'-dicyclohexylcarbodiimide/1-hydroxy-benzotriazole, 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium-tetrafluoroborate, 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium-tetrafluoroborate / 1-hydroxy-benzotriazole, N,N'-carbonyldiimidazole or triphenylphosphine/carbon tetrachloride, and optionally with the addition of a base such as pyridine, 4-dimethylamino pyridine, N-methyl-morpholine or triethylamine expediently at temperatures between 0 and 150°C, preferably at temperatures between 0 and 100°C.

The reaction of *an appropriate* reactive compound of general formula XIII such as esters, imidazolides or halides thereof is preferably performed in a solvent such as methylene chloride or ether and preferably in the presence of a tertiary organic base such as triethylamine, N-ethyl-diisopropylamine or N-methyl-morpholine at temperatures between 0 and 150°C, preferably at temperatures between 50 and 100°C.

The reaction of *an appropriate* reactive compound such as esters, isocyanates, imidazolides or halides thereof is preferably performed in a solvent such as methylene chloride or ether and optionally preferably in the presence of a tertiary organic base such as triethylamine, N-ethyl-diisopropylamine or N-methyl-morpholine at temperatures between 0 and 150°C, preferably at temperatures between 50 and 100°C.

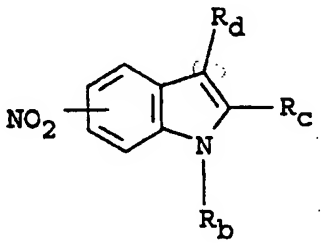
A compound of general formula I thus obtained which contains a reactive carboxyl function can then be converted as necessary into the desired compound of formula I with an appropriate amino acid derivative, which is done as described above,

or a compound of general formula I thus obtained which contains a reactive sulfonamide hydrogen atom can then be converted as necessary into the desired compound of general formula I with an appropriate halogen carboxylic acid derivative.

Subsequent reaction with *an appropriate* halogen carboxylic acid derivative is preferably performed in a solvent such as methylene chloride, acetonitrile, tetrahydrofuran, toluene, dimethylformamide or dimethylsulfoxide optionally in the presence of a base such as sodium hydride, potassium carbonate, potassium tert. butylate or N-ethyl-diisopropylamine at temperatures between 0 and 60°C.

i. To produce a compound of general formula I in which R_a is an amino group:

Reduction of a compound of the general formula



, (XVII)

in which
R_b through R_d are as initially defined:

Reduction is preferably by hydrogenolysis, e.g., with water in the presence of a catalyst such as palladium/carbon in a solvent such as methanol, ethanol, acetic acid ethylester, dimethylformamide, dimethylformamide/acetone or glacial acetic acid optionally with the addition of an acid such as hydrochloric acid at temperatures between 0 and 50°C but preferably at room temperature, and at a hydrogen pressure of 1 to 7 bar but preferably 3 to 5 bar.

If a compound of general formula I is obtained in accordance with the invention which contains a pyridinyl nitrogen atom, this compound can be quarternized by means of alkyation at the pyridine nitrogen atom, or

if a compound of general formula I containing an aromatically bound halogen atom is obtained, the halogen atom in this compound can be replaced by a hydrogen atom by means of dehalogenation.

The subsequent alkylation is expediently performed with a C_{1-3}-alkylhalide such as methylbromide or methyliodide preferably in a solvent such as methylene chloride, acetonitrile, tetrahydrofuran, toluene, dimethylformamide or dimethylsulfoxide optionally in the presence of a base such as sodium hydride, potassium carbonate, potassium tert. butylate or N-ethyl-diisopropylamine at temperatures between 0 and 60°C.

The subsequent dehalogenation is preferably performed hydrogenolytically, e.g., with water in the presence of a catalyst such as palladium/carbon or Raney nickel in a solvent such as methanol, ethanol, acetic acid ethylester, dimethylformamide, dimethylformamide/acetone or glacial acetic acid at temperatures between 0 and 50°C but preferably at room temperature, and at a hydrogen pressure of 1 to 7 bar but preferably 3 to 5 bar.

In the reactions described above, reactive groups such as hydroxy, carboxy, amino, alkylamino or imino groups can optionally be protected during the reaction by standard protective groups which are cleaved off again after the reaction.

For example, the trimethylsilyl, acetyl, benzoyl, tert. butyl, trityl, benzyl or tetrahydropyranyl group can be a protective radical for a hydroxy group,

the trimethylsilyl, methyl, ethyl, tert.butyl, benzyl or tetrahydropyranyl group can be a protective radical for a carboxyl group, and

the acetyl, trifluoroacetyl, benzoyl, ethoxycarbonyl, tert. butoxycarbonyl, benzyloxycarbonyl, benzyl, methoxybenzyl or 2,4-dimethoxybenzyl group can be a protective radical for an amino, alkylamino or imino group, and the phthalyl group can also be a protective radical for the amino group.

The subsequent optional cleavage of a protective radical is performed hydrolytically for example in an aqueous solvent, e.g., in water, isopropanol/water, tetrahydrofuran/water or dioxane/water, in the presence of an acid such as trifluoroacetic acid, hydrochloric acid or sulfuric acid or in the presence of an alkaline base such as lithium hydroxide, sodium hydroxide or potassium hydroxide or by means of ether splitting, e.g., in the presence of iodotrimethylsilane, at temperatures between 0 and 100°C, preferably at temperatures between 10 and 50°C.

The cleavage of a benzyl, methoxybenzyl or benzyloxy carbonyl radical is performed hydrogenolytically, however, e.g. with water in the presence of a catalyst such as palladium/carbon in a solvent such as methanol, ethanol, glacial acetic acid ethylester, dimethylformamide, dimethylformamide/acetone or glacial acetic acid optionally with the addition of an acid such as hydrochloric acid at temperatures between 0 and 50°C, but preferably at room temperature, and at a hydrogen pressure of 1 to 7 bar, but preferably 3 to 5 bar.

A methoxybenzyl group can also be split off in the presence of an oxidant such as cerium(IV) ammonium nitrate in a solvent such as methylene chloride, acetonitrile or acetonitrile/water at temperatures between 0 and 50°C, but preferably at room temperature.

A 2,4-dimethoxybenzyl radical, however, is preferably split off in trifluoroacetic acid in the presence of anisol.

A tert. butyl or tert. butyloxycarbonyl radical is preferably split off by treatment with an acid such as trifluoroacetic acid or hydrochloric acid optionally with the use of a solvent such as methylene chloride, dioxane or ether.

A phthalyl radical is preferably split off in the presence of hydrazine or a primary amine such as methylamine, ethylamine or n-butylamine in a solvent such as methanol, ethanol, isopropanol, toluene/water or dioxane at temperatures between 20 and 50°C.

An allyloxycarbonyl radical is split off by treatment with a catalytic amount of tetrakis-(triphenylphosphine)-palladium (O) preferably in a solvent such as tetrahydrofuran and preferably in the presence of an excess of a base such as morpholine or 1,3-dimedone at temperatures between 0 and 100°C, preferably at room temperature and under inert gas, or by treatment with a catalytic amount of tris-(triphenylphosphine)-rhodium(I) chloride in a solvent such as aqueous

ethanol and optionally in the presence of a base such as 1,4-diazabicyclo(2,2,2)octane at temperatures between 20 and 70°C.

The compounds of general formulas II through XVII used as starting substances and partially known in the literature are obtained by procedures known in the literature, and their production is described in the examples.

Thus, for example, a compound of general formula II is obtained by reacting an appropriate nitrile which, for its part, is expediently obtained by a procedure defined in this invention, and subsequent reaction of the nitrile thus obtained with an appropriate alcohol or mercaptane in the presence of hydrogen chloride or hydrogen bromide or with hydrogen sulfide and subsequent alkylation.

The compounds used as starting substances for this are obtained by acylation of an appropriately substituted indole and subsequent reaction of the indole thus obtained which is appropriately substituted at the phenyl ring, with an appropriate amine or by acylation of an indole already appropriately substituted by the R_a group.

A starting compound which carries an optionally monosubstituted amino group at the phenyl ring is obtained expediently by acylation of *an appropriate* nitro indole, subsequent reduction and optionally subsequent alkylation and/or arylation of the amino indole thus obtained.

The indole derivatives needed for this are obtained using procedures known in the literature, e.g., by ring closure of an appropriate acetal or dimethylaminovinylene.

The compounds of formula I obtained can also be separated into their enantiomers and/or diastereomers.

Thus, for example, the compounds of general formula I obtained which occur in racemates can be separated using familiar methods (see Allinger N.L. and Eliel E.L. in "Topics in Stereochemistry", Vol. 6, Wiley Interscience, 1971) into their optical antipodes and compounds of general formula I with at least 2 asymmetrical carbon atoms can be separated, due to their physical and chemical differences, by familiar methods, e.g., by chromatography and/or fractionated crystallization, into their diastereomers which, if they occur in a racemic form, can then be separated into the enantiomers as mentioned above.

Enantiomer separation is preferably performed by column separation on chiral phases or by recrystallization from an optically active solvent or by reaction with an optically active substance that, with the racemic compound, forms salts or derivatives such as, for example, esters or amides, and especially acids and their activated derivatives or alcohols, and separation of the diastereomeric salt mixture or derivative obtained in this way, e.g. based on different solubilities, with the free antipodes being released from the pure diastereomeric salts or derivatives under the effect of suitable agents. Particularly useful optically active acids are, for example, the D and L forms of tartaric acid or dibenzoyl tartaric acid, di-o-tolyl tartaric acid, malic acid, mandelic acid, camphor sulfonic acid, glutamic acid, aspartic acid or quinic acid. As an optically active alcohol, (+) or

(-) menthol can be considered for example and the (+) or (-) menthyloxycarbonyl radical can be considered as an optically active acyl radical in amides, for example.

The formula I compounds obtained can also be converted into their salts, and especially for pharmaceutical application, into their physiologically compatible salts with inorganic or organic acids. Acids for this purpose can be, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid or maleic acid.

If desired, the new formula I compounds thus obtained can then also be converted, if they contain a carboxy group, into their salts with inorganic or organic bases, and especially for pharmaceutical application into their physiologically compatible salts. Bases for this purpose can be, for example, sodium hydroxide, potassium hydroxide, cyclohexylamine, ethanolamine, diethanolamine and triethanolamine.

As already mentioned at the beginning, the new general formula I compounds and their salts have valuable properties. Thus the compounds of general formula I in which R_b or R_d contains a cyanophenyl group, provide valuable intermediate products for the production of the other compounds of general formula I, and the compounds of general formula I in which R_b or R_d contains an R_1NH-C(=NH)-phenyl group, as well as their tautomers, their stereoisomers and their physiologically compatible salts offer valuable pharmacological properties, and especially an antithrombotic effect due primarily to a thrombin-influencing action, for example a thrombin-inhibiting effect, a thrombin-time extending effect, an inhibiting effect on related serine proteases such as, for example, trypsin, urokinase factor VIIa, factor Xa, factor IX, factor XI and factor XII, and a fibrinogen-receptor antagonistic effect.

For example, the compounds

A = 3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-(2-hydroxycarbonylethyl)-N-phenyl-amide-hydrochloride,

B = 3-[3-(4-amidinophenyl)-propionyl]-N-hydroxycarbonylmethyl-N-(2-pyridylcarbonyl)-1-methyl-5-indolamine-hydrochloride

and

C = 3-[3-(4-amidinophenyl)-propionyl]-N-hydroxycarbonylmethyl-N-(4-thiazolylcarbonyl)-1-methyl-5-indolamine-hydrochloride

were tested as follows for their effect on thrombin time:

Material: Plasma, from human citrate blood.
Test-thrombin (bovine), 30 U/ml, Behring Werke, Marburg
Diethylbarbiturate acetate buffer, ORWH 60/61, Behring Werke, Marburg
Biomatic B10 Coagulometer, Sarstedt.

Performance:

Thrombin time was determined with a Biomatic B10 Coagulometer from the Sarstedt Company.

The test substance was placed into the test vessels prescribed by the manufacturer with 0.1 ml human citrate plasma and 0.1 ml diethylbarbiturate buffer (DBA buffer). The batch was incubated for one minute at 37°C. The coagulation reaction was started by adding 0.3 U of test thrombin in 0.1 ml DBA buffer. The time to the coagulation of the batch was measured with the thrombin input as required by the unit. Batches into which 0.1 ml DBA buffer was added served as controls.

According to the definition, the effective concentration of substance at which thrombin time was doubled compared with that of the controls was determined via a dose curve.

The following table contains the values found:

Substance	Thrombin time (ED_{200} in µM)
A	0.080
B	0.048
C	0.051

For example, no toxic side effects were observed in rats with the application of compounds A through C at a dose of 10 mg/kg i.v..

Because of their pharmacological properties, the new compounds and their physiologically compatible salts are suitable for the prevention and treatment of venous and arterial thrombotic diseases such as, for example, the treatment of deep leg vein thrombosis, the prevention of re-occlusions after bypass operations or angioplasty (PT(C)A), and occlusion in the case of peripheral arterial diseases such as pulmonary embolism, disseminated intravascular coagulation, the prophylaxis of coronary thrombosis, the prophylaxis of stroke and the prevention of shunt occlusion. The compounds of the invention are also suitable for antithrombotic assistance during thrombolytic treatment such as, for example, with rt-PA or streptokinase, for the prevention of long-term restenosis after PT(C)A, for the prevention of the metastasis and growth of coagulation-dependent tumors and fibrin-dependent inflammatory processes.

The dosage required to achieve an appropriate effect is expediently 0.1 to 30 mg/kg, preferably 0.3 to 10 mg/kg, with intravenous administration and 0.1 to 50 mg/kg, preferably 0.3 to 30 mg/kg with oral administration, 1 to 4 times daily in each case. For this purpose, the formula I compounds produced according to the invention can be incorporated, optionally in combination with other active substances, together with one or more inert standard vehicles and/or diluents,

e.g., corn starch, lactose, sucrose, microcrystalline cellulose, magnesium stearate, polyvinylpyrrolidone, citric acid, tartaric acid, water, water/ethanol, water/glycerine, water/sorbitol, water/polyethylene glycol, propylene glycol, cetylstearyl alcohol, carboxymethyl cellulose or fat-containing substances such as hard fat or suitable mixtures thereof, into standard galenic preparations such as tablets, pills, capsules, powder, suspensions or suppositories

The following examples are intended to illustrate the invention in more detail:

Abbreviations used:

CDI = N,N'-carbonyldiimidazole
DMF = dimethylformamide
DMSO = dimethylsulfoxide
HOBt = 1-hydroxy-1H-benzotriazole
TBTU = O-(benzotriazole-1-yl)-N,N,N',N'-bis(tetramethylene)-uronium-hexafluorophosphate
THF = tetrahydrofuran

Example 1

3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-ethoxycarbonylmethyl-N-ethyl-amide-hydrochloride

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a) 1-methylindole-5-carboxylic acid methylester

25 g (143 mmol) indole-5-carboxylic acid methylester are dissolved in 200 ml DMSO and mixed with 16.8 g (150 mmol) potassium tert. butylate at room temperature in portions for 30 minutes. The internal temperature rises to approx. 30°C. The mixture is then stirred for another 1 hour. The reaction solution turns green. 22.7 g (10 ml, 160 mmol) methyl iodide are then added in drops for 15 minutes, with the internal temperature being kept at 20°C by cooling. The solution is stirred for another 2 hours at room temperature. The color becomes lighter. The solution is poured into 1.2 liters ice water and the precipitate is drawn off; washed with water and dried at 60°C.
Yield: 26.9 g (99% of theory),
Melting point: 111-113°C.

b) 3-(4-cyanophenyl)-propionic acid chloride

300 g (2.29 mol) 4-cyanobenzaldehyde are dissolved in 560 ml pyridine, and 285 g (2.74 mol) malonic acid and 19.5 g (22.6 ml, 0.23 mol) piperidine are added successively. The internal temperature rises to 40°C and a clear solution forms. After 30 minutes of stirring, it is heated for another 2.5 hours to reflux. The reaction product precipitates out. It is then cooled to 40°C and poured onto a solution of 560 ml conc. hydrochloric acid in 3 liters of ice water. After 20 minutes of stirring, the precipitate is drawn off and washed twice with 1 liter of water each time.

Yield: 376 g (95% of theory),
Melting point: 260-268°C.

This raw product is poured into 5.4 liters of 1N potassium carbonate solution and mixed with 120 g of 5% palladium/carbon. The mixture is hydrated for 40 minutes at room temperature and a hydrogen pressure of 5 bar, neutralized with 500 ml concentrated hydrochloric acid and drawn off.
Yield: 291 g (74% of theory),
Melting point: 134-144°C.

3.3 g (10 mmol) of the carboxylic acid obtained are suspended in 100 ml chloroform and mixed with 5.9 g (3.9 ml, 50 mmol) thionyl chloride. 2 drops of DMF are added and the mixture is heated for 4.5 hours to reflux. A clear solution forms. The solvent is removed *in vacuo*, and the residue is stirred with ether and drawn off.
Yield: 3.47 g (99% of theory).

c) 3-[3-(4-cyanophenyl)-propionyl]-1-methylindole-5-carboxylic acid methylester

22.7 g (0.17 mol) aluminum trichloride are suspended in 150 ml 1,2-dichloromethane and mixed in portions with 29 g (0.15 mol) 3-(4-cyanophenyl)-propionic acid chloride with ice cooling so that the internal temperature does not exceed 6°C. The mixture is stirred for an hour with ice cooling and a clear solution forms. 26.9 g (0.142 mol) 1-methylindole-5-carboxylic acid methylester are then added in portions with ice cooling. The reaction solution mixture is stirred and is slowly allowed to warm up to room temperature. After 3 hours a precipitate forms, and 100 ml 1,2-dichloroethane are added for better stirring. After another 17 hours of stirring, the reaction solution is mixed with crushed ice under ice cooling.. The organic phase is then separated off and washed twice with water. After removal of the solvent *in vacuo*, it is stirred with ethanol and drawn off. The solid is heated with ethyl acetate and allowed to stand overnight at room temperature before being drawn off and dried at 80°C.
Yield: 30.4 g (62% of theory)
Melting point: 182-183°C.

d) 3-[3-(4-cyanophenyl)-propionyl]-1-methylindole-5-carboxylic acid chloride

25.1 g (72.5 mmol) 3-[3-(4-cyanophenyl)-propionyl]-1-indole-5-carboxylic acid methylester are suspended in 800 ml acetonitrile and mixed with 40 g (28.5 ml, 0.20 mol) iodine trimethylsilane. The reaction solution is heated to reflux for 5 hours in darkness and is then allowed to stand overnight at room temperature. Approx. 500 ml of solvent are removed *in vacuo*, and 1 liter ethyl acetate and 10 ml of water are added, followed by extraction with a total of 1 liter of 0.5N caustic soda solution. The aqueous phase is washed with ethyl acetate and then acidified with 6N hydrochloric acid. The resulting precipitate is drawn off, washed again with water, a little cold ethanol and acetone, and dried at 100°C.
Yield: 21 g (87% of theory).

3.3 g (10 mmol) of the 3-[3-(4-cyanophenyl)-propionyl]-1-methylindole-5-carboxylic acid thus obtained are heated to reflux for 4.5 hours in 100 ml chloroform with 5.9 g (3.9 ml, 50 mmol) thionyl chloride and 2 drops of DMF. The

solvent is then removed *in vacuo*, and the residue is stirred with ether and dried *in vacuo*.
Yield: 3.47 g (99% of theory).

e) Ethylaminoacetic acid ethylester hydrochloride

15.8 g (21.3 ml, 0.15 mol) freshly condensed ethylamine are dissolved at -12°C in 250 ml THF. 25 g (16.3 ml, 0.15 mol) bromoacetic acid ethylester are added in drops with stirring. The reaction solution is allowed to stand overnight at room temperature. The precipitate is drawn off and the solvent is removed from the filtrate *in vacuo*. The residue is chromatographed on silica gel (ethyl acetate/methanol = 19:1). The yellow oil thus obtained is dissolved in ether and acidified with ethereal hydrochloric acid with stirring. After being allowed to stand overnight, it is drawn off and dried.
Yield: 14.0 g (56% of theory)
Melting point: 134-137°C
$C_6H_{13}NO_2 \times HCl$ (167.64)
Calculated: C 42.99 H 8.42 N 8.36 Cl 21.15
Found: C 42.97 H 8.35 N 8.54 Cl 21.12

f) 3-[3-(4-cyanophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-ethoxy-carbonylmethyl-N-ethyl-amide

1.05 g (3.00 mmol) of 3-[3-(4-cyanophenyl)-propionyl]-1-methylindole-5-carboxylic acid chloride dissolved in 15 ml dichloromethane are added in drops at room temperature to a solution of 500 mg (3.6 mmol) ethylaminoacetic acid ethylester hydrochloride and 1.2 g (1.7 ml, 12 mmol) triethylamine in 15 ml dichloromethane. The mixture is stirred overnight at room temperature. After removal *in vacuo* of the solvent, the residue is absorbed in ethyl acetate/water and washed with water, 0.2N hydrochloric acid and again with water. The organic phase is evaporated after drying over sodium sulfate and the oily residue is chromatographed on silica gel (petroleum ether/ethyl acetate = 1:9). After removal of the solvent, the residue thus obtained is triturated with ether, drawn off and dried *in vacuo* at 60°C.
Yield: 700 mg (52% of theory)
Melting point: 154-156°C
$C_{26}H_{27}N_3O_4$ (445.52)
Calculated: C 70.10 H 6.11 N 9.43
Found: C 69.86 H 6.14 N 9.37

g) 3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-ethoxy-carbonylmethyl-N-ethyl-amide hydrochloride

Hydrogen chloride gas is introduced into 25 ml ethanol at -5°C to saturation. 680 g (1.53 mmol) 3-[3-(4-cyanophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-ethoxycarbonylmethyl-N-ethyl-amide are added with stirring and the mixture is allowed to warm up to room temperature overnight. The solvent is then removed

in vacuo and the residue is absorbed in 30 ml absolute ethanol. 1.5 g of finely ground ammonium carbonate are added and the mixture is stirred overnight at room temperature. After the solvent is removed *in vacuo*, the residue is chromatographed on silica gel (dichloromethane/methanol = 8:2). The foam thus obtained is stirred with ether and dried *in vacuo* at 60°C.
Yield: 540 g (68% of theory)
Melting point: 145-160°C
$C_{26}H_{30}N_4O_4$ (462.55)
Mass spectrum: $(M+H)^+ = 463$
$C_{26}H_{30}N_4O_4 \times HCl \times 1.5\ H_2O$ (526.04)
Calculated: C 59.37 H 6.51 N 10.65
Found: C 59.45 H 6.32 N 10.60

Example 2

3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-hydroxycarbonylmethyl-N-ethyl-amide-hydrochloride

---

368 mg (0.70 mmol) 3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-ethoxycarbonylmethyl-N-ethyl-amide-hydrochloride are dissolved in 10 ml ethanol and 2.1 ml 1N caustic soda solution are added. The mixture is stirred at room temperature for 2.5 hours and diluted with water to a volume of 40 ml. It is then adjusted to pH 7.2 with dilute hydrochloric acid. The product thus precipitated is drawn off, again suspended in dioxane and mixed with 0.1N hydrochloric acid until there is a clear solution. After the solvent is removed *in vacuo*, the residue is stirred with ether, drawn off and dried *in vacuo* at 60°C.
Yield: 270 mg (80% of theory)
Melting point: 135-140°C
$C_{24}H_{26}N_4O_4$
Mass spectrum: $(M+H)^+ = 435$

Example 3

3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-ethoxycarbonylmethyl-N-propyl-amide-hydrochloride

---

Produced as in example 1 from 3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-ethoxycarbonylmethyl-N-propyl-amide with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 71% of theory
Melting point: 150-160°C
$C_{27}H_{32}N_4O_4$ (476.58)
Mass spectrum: $(M+H)^+ = 477$
$C_{27}H_{32}N_4O_4 \times HCl \times H_2O$ (531.06)
Calculated: C 61.07 H 6.64 N 10.55
Found: C 60.75 H 6.53 N 10.65

Example 4

3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-hydroxycarbonylmethyl-N-propyl-amide-hydrochloride

---

Produced as in example 2 by saponification of 3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-ethoxycarbonylmethyl-N-propyl-amide hydrochloride.
Yield: 77% of theory
Melting point: 236-239°C (decomp.)
$C_{25}H_{28}N_4O_4$ (448.53)
Mass spectrum: $(M+H)^+ = 449$
$C_{25}H_{28}N_4O_4 \times HCl \times H_2O$ (503.00)
Calculated: C 59.70 H 6.21 N 11.14 Cl 7.05
Found: C 59.74 H 6.35 N 11.10 Cl 7.10

Example 5

3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-ethoxycarbonylmethylaminocarbonylmethyl-N-propyl-amide-hydrochloride

---

a) 3-[3-(4-cyanophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-hydroxycarbonylmethyl-N-propyl-amide

1.9 g (4.1 mmol) 3-[3-(4-cyanophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-ethoxycarbonylmethyl-N-propyl-amide (produced as in example 1) are dissolved in 100 ml ethanol and mixed with 12.3 ml 1N caustic soda solution. The mixture is stirred for 2.5 hours at room temperature and then neutralized with 1N hydrochloric acid. Water is added, and the solution is stirred overnight, then cooled with ice and the precipitate is drawn off.
Yield: 1.7 g (96% of theory)
Melting point: 173-175°C

b) 3-[3-(4-cyanophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-ethoxycarbonylmethylaminocarbonylmethyl-N-propyl-amide

1.7 g (3.9 mmol) 3-[3-(4-cyanophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-hydroxycarbonylmethyl-N-propyl-amide are dissolved in 50 ml THF and mixed with stirring with 0.87 g (0.95 ml, 8.6 mmol) N-methylmorpholine. The solution is cooled to -30°C; 0.62 ml (4.6 mmol) chloroformic acid isobutylester is added in drops and the solution is stirred for 45 minutes at room temperature. 0.6 g (4.3 mmol) glycine ethylester hydrochloride is then added at -30°C and the solution is slowly heated to room temperature overnight. The solvent is removed *in vacuo*. After absorption in water, the aqueous phase is extracted with dichloromethane. The organic phase is washed again with water and dried over

magnesium sulfate. After removal of the solvent *in vacuo*, crystallization is performed from ethyl acetate.
Yield: 1.1 g (55% of theory)
Melting point: 121-123°C
$C_{29}H_{32}N_4O_5$ (516.60)
Mass spectrum: $M^+ = 516$

c) 3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-ethoxycarbonylmethylaminocarbonylmethyl-N-propyl-amide-hydrochloride

Produced as in example 1 from 3-[3-(4-cyanophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-ethoxycarbonylmethylaminocarbonylmethyl-N-propyl-amide with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 69% of theory
Melting point: 136-138°C
$C_{29}H_{35}N_5O_5$ (533.63)
Mass spectrum: $(M+H)^+ = 534$

Example 6

3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-hydroxycarbonylmethylaminocarbonylmethyl-N-propyl-amide hydrochloride

---

Produced as in example 2 by saponification of 3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-ethoxycarbonylmethylaminocarbonylmethyl-N-propyl-amide hydrochloride.
Yield: 63% of theory
Melting point: 198-200°C
$C_{27}H_{31}N_5O_5$ (505.58)
Mass spectrum: $(M+H)^+ = 506$

Example 7

3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-ethoxycarbonylmethyl-N-butyl-amide hydrochloride

---

Produced as in example 1 from 3-[3-(4-cyanophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-ethoxycarbonylmethyl-N-butyl-amide with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 78% of theory
Melting point: 242-249°C (decomp.)
$C_{28}H_{34}N_4O_4$ (490.61)
Mass spectrum: $(M+H)^+ = 491$
$C_{28}H_{34}N_4O_4 \times HCl \times H_2O$ (545.09)
Calculated: C 61.70 H 6.84 N 10.28
Found: C 61.98 H 6.60 N 10.47

Example 8

3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-hydroxycarbonylmethyl-N-butyl-amide hydrochloride

---

Produced as in example 2 by saponification of 3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-ethoxycarbonylmethyl-N-butyl-amide hydrochloride.
Yield: 78% of theory
Melting point: 240-241°C (decomp.)
$C_{26}H_{30}N_4O_4$ (462.55)
Mass spectrum: $(M+H)^+ = 463$
$C_{26}H_{30}N_4O_4 \times HCl \times H_2O$ (517.03)
Calculated: C 60.40 H 6.43 N 10.84 Cl 6.86
Found: C 60.30 H 6.58 N 10.58 Cl 6.85

Example 9

3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-ethoxycarbonylmethyl-N-pentyl-amide hydrochloride

---

Produced as in example 1 from 3-[3-(4-cyanophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-ethoxycarbonylmethyl-N-pentyl-amide with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 67% of theory
Melting point: 120-130°C
$C_{29}H_{36}N_4O_4$ (504.64)
Mass spectrum: $(M+H)^+ = 505$
$C_{29}H_{36}N_4O_4 \times HCl \times H_2O$ (559.12)
Calculated: C 62.30 H 7.03 N 10.02
Found: C 62.30 H 6.89 N 10.17

Example 10

3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-hydroxycarbonylmethyl-N-pentyl-amide hydrochloride

---

Produced as in example 2 by saponification of 3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-ethoxycarbonylmethyl-N-pentyl-amide hydrochloride.
Yield: 81% of theory
Melting point: 247-248°C (decomp.)
$C_{27}H_{32}N_4O_4$ (476.58)
Mass spectrum: $(M+H)^+ = 477$

Example 11

3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-ethoxycarbonylmethyl-N-isopropyl-amide hydrochloride

---

Produced as in example 1 from 3-[3-(4-cyanophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-ethoxycarbonylmethyl-N-isopropyl-amide with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 68% of theory
Melting point: 183-187°C
$C_{27}H_{32}N_4O_4$ (476.58)
Mass spectrum: $(M+H)^+ = 477$

Example 12

3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-hydroxycarbonylmethyl-N-isopropyl-amide hydrochloride

---

Produced as in example 2 by saponification of 3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-ethoxycarbonylmethyl-N-isopropyl-amide hydrochloride.
Yield: 81% of theory
Melting point: 206-209°C (decomp.)
$C_{25}H_{28}N_4O_4$ (448.53)
Mass spectrum: $(M+H)^+ = 449$
$C_{25}H_{28}N_4O_4 \times HCl \times 1.5\ H_2O$ (512.01)
Calculated: C 58.65 H 6.30 N 10.94
Found: C 58.85 H 6.22 N 10.62

Example 13

3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-ethoxycarbonylmethyl-N-cyclopropyl-amide hydrochloride

---

Produced as in example 1 from 3-[3-(4-cyanophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-ethoxycarbonylmethyl-N-cyclopropyl-amide with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 72% of theory
Melting point: 140-160°C
$C_{27}H_{30}N_4O_4$ (474.57)
Mass spectrum: $(M+H)^+ = 475$
$C_{27}H_{30}N_4O_4 \times HCl \times 1.5\ H_2O$ (538.05)
Calculated: C 60.27 H 6.37 N 10.41
Found: C 60.30 H 6.49 N 10.43

Example 14

3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-hydroxycarbonylmethyl-N-cyclopropyl-amide hydrochloride

---

Produced as in example 2 by saponification of 3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-ethoxycarbonylmethyl-N-cyclopropyl-amide hydrochloride.
Yield: 75% of theory
Melting point: 278-280°C
$C_{25}H_{26}N_4O_4$ (446.51)
Mass spectrum: $(M+H)^+ = 447$

Example 15

3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-ethoxycarbonylmethyl-N-cyclohexyl-amide-hydrochloride

---

Produced as in example 1 from 3-[3-(4-cyanophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-ethoxycarbonylmethyl-N-cyclohexyl-amide with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 63% of theory
Melting point: 170-200°C (sintering)
$C_{30}H_{36}N_4O_4$ (516.65)
Mass spectrum: $(M+H)^+ = 517$
$C_{30}H_{36}N_4O_4 \times HCl \times 2\ H_2O$ (589.14)
Calculated: C 61.16 H 7.01 N 9.51
Found: C 61.18 H 6.95 N 9.46

Example 16

3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-hydroxycarbonylmethyl-N-cyclohexyl-amide hydrochloride

---

Produced as in example 2 by saponification of 3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-ethoxycarbonylmethyl-N-cyclohexyl-amide hydrochloride.
Yield: 72% of theory
Melting point: 245-247°C (decomp.)
$C_{28}H_{32}N_4O_4$ (488.59)
Mass spectrum: $(M+H)^+ = 489$
$C_{28}H_{32}N_4O_4 \times HCl \times 1.5\ H_2O$ (552.08)
Calculated: C 60.92 H 6.57 N 10.15
Found: C 61.00 H 6.62 N 10.01

Example 17

3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-(1-pyrrolidine)-amide

---

Produced as in example 1 from 3-[3-(4-cyanophenyl)-propionyl]-1-methylindole-5-carboxylic acid-(1-pyrrolidine)-amide with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 67% of theory
Melting point: 215-220°C
$C_{24}H_{26}N_4O_2$ (402.50)
Mass spectrum: $(M+H)^+ = 403$
$C_{24}H_{26}N_4O_2 \times HCl \times 1.5\ H_2O$ (465.99)
Calculated: C 61.86 H 6.49 N 12.02
Found: C 61.41 H 6.34 N 11.72

Example 18

3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-ethoxycarbonylmethyl-N-dimethylaminoethyl-amide dihydrochloride

---

Produced as in example 1 from 3-[3-(4-cyanophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-ethoxycarbonylmethyl-N-dimethylaminoethyl-amide with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 59% of theory
Melting point: 147-150°C
$C_{28}H_{35}N_5O_4$ (505.62)
Mass spectrum: $(M+H)^+ = 506$

Example 19

3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-hydroxycarbonylmethyl-N-dimethylaminoethyl-amide dihydrochloride

---

Produced as in example 2 by saponification of 3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-ethoxycarbonylmethyl-N-dimethylaminoethyl-amide dihydrochloride.
Yield: 68% of theory
Melting point: 210-220°C
$C_{26}H_{31}N_5O_4$ (477.57)
Mass spectrum: $(M+H)^+ = 478$

Example 20

3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-phenyl-amide hydrochloride

---

Produced as in example 1 from 3-[3-(4-cyanophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-phenyl-amide with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 61% of theory
Melting point: 219-225°C
$C_{26}H_{24}N_4O_2$ (424.51)
Mass spectrum: $(M+H)^+ = 425$

Example 21

3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-ethoxycarbonylmethyl-N-phenyl-amide hydroiodide

---

1.4 g (2.84 mmol) 3-[3-(4-cyanophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-ethoxycarbonylmethyl-N-phenyl-amide are dissolved in 25 ml pyridine and mixed with 850 mg (1.2 ml, 8.5 mmol) triethylamine. Approx. 2 g hydrogen sulfide gas are introduced with ice cooling. The mixture is stirred overnight at room temperature. Nitrogen is then passed through the solution and the solvent is removed *in vacuo*. The residue is dissolved in dichloromethane and the solution is washed with water and dilute hydrochloric acid. After drying over magnesium sulfate and removal of the solvent *in vacuo*, 1.45 g of solid substance is obtained that is suspended in 50 ml acetone and stirred overnight with 4 g (28 mmol) methyliodide. After the solvent is removed *in vacuo*, 1.95 g of a foamy product is obtained. This is suspended in a mixture of 70 ml ethanol and 20 ml dichloromethane and mixed with 1.3 g (17 mmol) ammonium acetate. The mixture is stirred overnight, then heated for another 8 hours to 40°C. The solvent is removed *in vacuo* and the residue is chromatographed on silica gel (dichloromethane/methanol = 17:3). The product thus obtained is stirred with ether.
Yield: 1.3 g (69% of theory)
Melting point: 148-155°C (decomp.)
$C_{30}H_{30}N_4O_4$ (510.60)

Mass spectrum: $(M+H)^+ = 511$

Example 22

3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-hydroxycarbonylmethyl-N-phenyl-amide hydroiodide

---

Produced as in example 2 by saponification of 3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-ethoxycarbonylmethyl-N-phenyl-amide hydroiodide in dioxane.
Yield: 92% of theory
Melting point: 247-249°C (decomp.)
$C_{28}H_{26}N_4O_4$ (482.54)
Mass spectrum: $(M+H)^+ = 483$

Example 23

3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-(2-ethoxycarbonylethyl)-N-phenyl-amide hydroiodide

---

Produced as in example 21 from 3-[3-(4-cyanophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-(2-ethoxycarbonylethy)l-N-phenyl-amide with hydrogen sulfide, methyl iodide and ammonium acetate.
Yield: 54% of theory
Melting point: 140-150°C
$C_{31}H_{32}N_4O_4$ (524.63)
Mass spectrum: $(M+H)^+ = 525$

Example 24

3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-(2-hydroxycarbonylethyl)-N-phenyl-amide hydrochloride

---

Produced as in example 2 from 3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-(2-ethoxycarbonylethy)l-N-phenyl-amide hydroiodide with caustic soda solution and dilute hydrochloric acid.
Yield: 73% of theory
Melting point: 277-279°C (decomp.)
$C_{29}H_{28}N_4O_4$ (496.58)
Mass spectrum: $(M+H)^+ = 497$
$C_{29}H_{28}N_4O_4 \times HCl \times H_2O$ (551.05)
Calculated: C 63.21 H 5.67 N 10.17 Cl 6.43
Found: C 63.18 H 5.62 N 10.19 Cl 6.56

Example 25

3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-ethoxycarbonylmethyl-N-(8-quinolinyl)-amide hydroiodide

---

Produced as in example 21 from 3-[3-(4-cyanophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-ethoxycarbonylmethyl-N-(8-quinolinyl)-amide with hydrogen sulfide, methyl iodide and ammonium acetate.

Yield: 56% of theory
Melting point: 200-205°C (decomp.)
$C_{33}H_{31}N_5O_4$ (561.65)
Mass spectrum: $(M+H)^+ = 562$

Example 26

3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-hydroxycarbonylmethyl-N-(8-quinoliny)l-amide dihydrochloride

---

Produced as in example 2 by saponification of 3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-ethoxycarbonylmethyl-N-(8-quinolinyl) -amide hydroiodide with caustic soda solution, followed by treatment with dilute hydrochloric acid.
Yield: 84% of theory
Melting point: 190-195°C (decomp.)
$C_{31}H_{27}N_5O_4$ (533.60)
Mass spectrum: $(M+H)^+ = 534$

Example 27

3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-ethoxycarbonylmethyl-N-(2-pyridyl)-amide hydrochloride

---

a) 3-[3-(4-cyanophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-ethoxycarbonylmethyl-N-(2-pyridyl)-amide

1.4 g (4.0 mmol) of 3-[3-(4-cyanophenyl)-propionyl]-1-methylindole-5-carboxylic acid chloride are dissolved in a protective gas atmosphere in 30 ml dichloromethane as in example 1f, and mixed with 880 mg (0.63 ml, 4.4 mmol) iodine trimethylsilane at 0°C. The solvent is removed *in vacuo*, the residue is dissolved in 10 ml dichloromethane and the solution thus obtained is added with ice cooling to a solution of 540 mg (3.0 mmol) N-(2-pyridyl)-glycine ethylester and 1.55 g (2.1 ml, 12 mmol) ethyl-diisopropylamine in 10 ml dichloromethane. After 3 hours of stirring at room temperature, the mixture is washed with water and dried over magnesium sulfate. The solvent is removed *in vacuo*. The residue

obtained is chromatographed on silica gel (dichloromethane.ethyl acetate = 3:1) and triturated with ethyl acetate.
Yield: 940 mg (48% of theory)
Melting point: 181-182 °C
$C_{29}H_{26}N_4O_4$ (494.55)
Calculated: C 70.43 H 5.30 N 10.93
Found: C 70.06 H 5.36 N 11.16

b) 3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-ethoxycarbonylmethyl-N-(2-pyridyl)-amide-hydrochloride

Produced as in example 1g from 3-[3-(4-cyanophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-ethoxycarbonylmethyl-N-(2-pyridyl)-amide
with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 77% of theory
Melting point: 155-160 °C
$C_{29}H_{29}N_5O_4$ (511.59)
Mass spectrum: $(M+H)^+ = 512$
$C_{29}H_{29}N_5O_4 \times HCl \times 1.5\ H_2O$ (575.07)
Calculated: C 60.57 H 5.78 N 12.18
Found: C 60.83 H 5.70 N 11.95

Example 28

3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-hydroxycarbonylmethyl-N-(2-pyridyl)-amide-hydrochloride

---

Produced as in example 2 by saponification of 3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-ethoxycarbonylmethyl-N-(2-pyridyl)-amide hydrochloride.
Yield: 73% of theory
Melting point: 190-200 °C (decomp.)
$C_{27}H_{25}N_5O_4$ (483.53)
Mass spectrum: $(M+H)^+ = 484$

Example 29

3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-(2-ethoxycarbonylethyl)-N-(2-pyridyl)-amide-hydrochloride

---

Produced as in example 1 from 3-[3-(4-cyanophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-(2-methoxycarbonylethyl-N-(2-pyridyl)-amide
with ethanolic hydrochloric acid and ammonium carbonate with transesterification.
Yield: 76% of theory
Melting point: 135-140 °C
$C_{30}H_{31}N_5O_4$ (525.61)

Mass spectrum: $(M+H)^+ = 526$

Example 30

3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-(2-hydroxycarbonylethyl)-N-(2-pyridyl)-amide-hydrochloride.

Produced as in example 2 by saponification of 3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-(2-ethoxycarbonylethyl)-N-(2-pyridyl)-amide hydrochloride.
Yield: 71% of theory
Melting point: 170°C (decomp.)
$C_{25}H_{27}N_5O_4$ (497.56)
Mass spectrum: $(M+H)^+ = 498$

Example 31

3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-(3-ethoxycarbonylpropyl)-N-(2-pyridyl)-amide-hydroiodide

---

Produced as in example 21 from 3-[3-(4-cyanophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-(3-ethoxycarbonylpropyl)-N-(2-pyridyl)-amide
with hydrogen sulfide, methyl iodide and ammonium acetate.
Yield: 35% of theory
Melting point: 50-55°C
$C_{31}H_{33}N_5O_4$ (539.64)
Mass spectrum: $(M+H)^+ = 540$

Example 32

3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-(3-hydroxycarbonylpropyl)-N-(2-pyridyl)-amide-hydrochloride

---

250 mg (0.36 mml) 3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-(3-ethoxycarbonylpropyl)-N-(2-pyridyl)-amide hydroiodide
are stirred in 6 ml 6N hydrochloric acid for 48 hours at room temperature. The solution is drawn off from the insoluble part and the solvent is removed from the filtrate *in vacuo*. The residue is recrystallized from acetone.
Yield: 120 mg (59% of theory)
Melting point: 225-228 °C
$C_{29}H_{29}N_5O_4$ (511.59)
Mass spectrum: $(M+H)^+ = 512$

Example 33

3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-ethoxycarbonylmethyl-N-(3-pyridyl)-amide-hydrochloride

---

Produced as in example 1 from 3-[3-(4-cyanophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-ethoxycarbonylmethyl-N-(3-pyridyl)-amide with ethanolic hydrochloric acid and ammonium carbonate.

Yield: 77% of theory
Melting point: 165-170 °C (sinters starting at 145°C)
$C_{29}H_{29}N_5O_4$ (511.59)
Mass spectrum: $(M+H)^+ = 512$
$C_{29}H_{29}N_5O_4 \times HCl \times 2\ H_2O$ (584.08)
Calculated: C 59.64 H 5.87 N 11.99
Found: C 59.45 H 5.78 N 11.73

Example 34

3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-hydroxycarbonylmethyl-N-(3-pyridyl)-amide-dihydrochloride

---

Produced as in example 2 by saponification of 3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-ethoxycarbonylmethyl-N-(3-pyridyl)-amide hydrochloride.
Yield: 67% of theory
Melting point: 208-210 °C
$C_{27}H_{25}N_5O_4$ (483.53)
Mass spectrum: $(M+H)^+ = 484$
$C_{27}H_{25}N_5O_4 \times 2\ HCl \times 0.5\ H_2O$ (565.47)
Calculated: C 57.35 H 4.99 N 12.39
Found: C 57.30 H 5.24 N 12.10

Example 35

3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-ethoxycarbonylmethyl-N-(4-pyrimidinyl)-amide-hydroiodide

---

Produced as in example 21 from 3-[3-(4-cyanophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-ethoxycarbonylmethyl-N-(4-pyrimidinyl)-amide with hydrogen sulfide, methyl iodide and ammonium acetate.
Yield: 53% of theory
Melting point: 200-205 °C (sinters starting at 150°C)
$C_{28}H_{28}N_6O_4$ (512.57)
Mass spectrum: $(M+H)^+ = 513$

Example 36

3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-(2-ethoxycarbonylethyl)-N-(4-pyrimidinyl)-amide-hydroiodide

---

Produced as in example 21 from 3-[3-(4-cyanophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-(2-ethoxycarbonylethyl)-N-(4-pyrimidinyl)-amide with hydrogen sulfide, methyl iodide and ammonium acetate.

Yield: 61% of theory
Melting point: 145-150 °C (sinters starting at 130°C)
$C_{29}H_{30}N_6O_4$ (526.60)
Mass spectrum: $(M+H)^+ = 527$

Example 37

3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-(2-tert.butoxycarbonylethyl)-N-(4-pyrimidine)-amide-hydroiodide

---

Produced as in example 21 from 3-[3-(4-cyanophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-(2-tert.butoxycarbonylethyl-N-(4-pyrimidinyl)-amide with hydrogen sulfide, methyl iodide and ammonium acetate.
Yield: 43% of theory
Melting point: 180-185 °C (decomp.)
$C_{31}H_{34}N_6O_4$ (554.65)
Mass spectrum: $(M+H)^+ = 555$

Example 38

3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-(2-hydroxycarbonylethyl-N-(4-pyrimidinyl)-amide-hydrochloride

---

Produced as in example 32 by acidic hydrolysis of 3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-(2-tert.butoxycarbonylethyl)-N-(pyrimidin-4-yl)-amide hydroiodide with 6N hydrochloric acid.
Yield: 33% of theory
Melting point: 200-210 °C (decomp.)
$C_{27}H_{26}N_6O_4$ (498.55)
Mass spectrum: $(M+H)^+ = 499$

Example 39

3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-(3-methoxycarbonylpropyl)-N-(pyrimidin-4-yl)-amide-hydroiodide

---

Produced as in example 21 from 3-[3-(4-cyanophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-(3-methoxycarbonylpropyl)-N-(pyrimidin-4-yl)-amide with hydrogen sulfide, methyl iodide and ammonium acetate.
Yield: 34% of theory
Melting point: 58-60°C
$C_{29}H_{30}N_6O_4$ (526.60)
Mass spectrum: $(M+H)^+ = 527$

Example 40

3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-(ethoxycarbonylmethyl)-N-(2-pyrimidine)-amide-hydrochloride

---

Produced as in example 1 from 3-[3-(4-cyanophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-(ethoxycarbonylmethyl)-N-(2-pyrimidinyl)-amide with ethanolic hydrochloric acid and ammonium carbonate as an inseparable 1:1 mixture of 3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid ethylester and the title compound.
Yield: 64% of theory
Melting point: 160-170 °C
$C_{28}H_{28}N_6O_4$ (512.57)
Mass spectrum: $(M+H)^+ = 513$

Example 41

3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-hydroxycarbonylmethyl-N-(2-pyrimidinyl)-amide-hydrochloride

---

Produced as in example 2 by saponification of 3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-(ethoxycarbonylmethy)l-N-(2-pyrimidinyl)-amide hydrochloride.
Yield: 40% of theory
Melting point: 230 °C (decomp.)
$C_{26}H_{24}N_6O_4$ (484.52)
Mass spectrum: $(M+H)^+ = 485$

Example 42

3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-(2-ethoxycarbonylethyl)-N-(3-pyridazinyl)-amide-hydroiodide

---

Produced as in example 21 from 3-[3-(4-cyanophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-(2-ethoxycarbonylethyl)-N-(3-pyridazinyl)-amide with hydrogen sulfide, methyl iodide and ammonium acetate.
Yield: 29% of theory
Melting point: 140-155 °C (sintering)
$C_{29}H_{30}N_6O_4$ (526.60)
Mass spectrum: $(M+H)^+ = 527$

Example 43

3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-(2-hydroxycarbonylethyl)-N-(3-pyridazinyl)-amide-hydrochloride

---

Produced as in example 2 by saponification of 3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-(2-ethoxycarbonylethyl)-N-(3-pyridazinyl)-amide hydroiodide.
Yield: 52% of theory
Melting point: > 165°C decomp.
$C_{27}H_{26}N_6O_4$ (498.54)
Mass spectrum: $(M+H)^+ = 499$

Example 44

3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-ethoxycarbonylmethyl)-N-methyl-amide-hydrochloride

---

Produced as in example 1 from 3-[3-(4-cyanophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-ethoxycarbonylmethyl)-N-methyl-amide with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 76% of theory
Melting point: 96-98°C
$C_{25}H_{28}N_4O_4$ (448.53)
Mass spectrum: $(M+H)^+ = 449$

Example 45

3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-hydroxycarbonylmethyl)-N-methyl-amide-hydrochloride

---

Produced as in example 2 by saponification of 3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-ethoxycarbonylmethyl)-N-methyl-amide hydrochloride.
Yield: 47% of theory
Melting point: 249-251°C
$C_{23}H_{24}N_4O_4$ (420.47)
Mass spectrum: $(M+H)^+ = 421$

Example 46

3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-carboxylic acid-N-(4-chlorophenyl)-N-methoxycarbonylmethyl)-amide-hydrochloride

---

a) 1-trifluoroacetylindoline-5-sulfonic acid-N-(4-chlorophenyl)-N-ethoxycarbonylmethyl-amide

8.4 ml (12.6 g, 60 mmol) trifluoroacetic acid anhydride are added in drops to a solution of 6.0 g (50 mmol) indoline in 30 ml dichloromethane at room temperature. The solution is stirred for 30 minutes at room temperature and then washed with water and dried over magnesium sulfate. The solvent is removed *in vacuo*. The residue is added in portions at 0-4°C for 25 minutes to 6.9 ml (12.1 g, 104 mmol) chlorosulfonic acid.. The solution is stirred for 30 minutes at 0°C, then for 18 hours at room temperature and for 8 hours at 70°C. The thick reaction solution is poured over ice and extracted with ethyl acetate. The organic phase is dried over magnesium sulfate and the solvent is removed *in vacuo*. After further rapid chromatic purification on silica gel, the product obtained is dissolved in 20 ml pyridine and mixed with 4.4 g (21 mmol) N-(4-chlorophenyl)-glycine ethylester. The solution is heated for 2 hours to 100°C, the solvent is then removed *in vacuo* and water and dilute hydrochloric acid are added. After extraction with ethyl acetate, the organic phase is dried over magnesium sulfate and chromatographed for further purification on silica gel (toluene/ethyl acetate = 7:3).
Yield: 7.2 g (29% of theory)

b) Indole-5-sulfonic acid-N-(4-chlorophenyl)-N-hydroxycarbonylmethyl-amide

7.1 g (15 mmol) 1-trifluoroacetyl indoline-5-sulfonic acid-N-(4-chlorophenyl)-N-ethoxycarbonylmethyl-amide are dissolved in a mixture of 220 ml dioxane and 220 ml methanol and stirred at room temperature with 60 ml 1N caustic soda solution overnight. The solvent is removed *in vacuo* and the mixture is absorbed in dichloromethane and a little methanol. After drying over magnesium sulfate, it is evaporated to dryness. The residue is dissolved in 40 ml dioxane and mixed in portions with 4.5 g (20 mmol) 2,3-dichloro-5,6-dicyanobenzoquinone at room temperature. The solution is stirred for 4 hours at room temperature and then drawn off from the insoluble portion. The filtrate is concentrated by evaporation to dryness and chromatographed on silica gel (dichloromethane/ethanol = 100:0 to 92:8).
Yield: 1.8 g (33% of theory).

c) 1-methylindole-5-sulfonic acid-N-(4-chlorophenyl)-N-methoxycarbonylmethyl-amide

140 mg (3.2 mmol) sodium hydride are added to a solution of 0.6 g (1.6 mmol) indole-5-sulfonic acid-N-(4-chlorophenyl)-N-hydroxycarbonylmethyl-amide in 10 ml DMSO under nitrogen at room temperature. The mixture is stirred for 1.5 hours. 2 ml (3 g, 22 mmol) methyl iodide are added and the mixture is stirred for another 1.5 hours. It is then poured onto 150 ml ice water and extracted with ethyl acetate. The organic phase is dried over magneisum sulfate and concentrated by evaporation to dryness. The residue thus obtained is chromatographed on silica gel (toluene/ethyl acetate = 9:1).
Yield: 430 mg (69% of theory)

d) 3-[3-(4-cyanophenyl)-propionyl]-1-methylindole-5-sulfonic acid-N-(4-chlorophenyl)-N-methoxycarbonylmethyl-amide

As in example 1c, 900 mg (2.3 mmol) 1-methylindole-5-sulfonic acid-N-(4-chlorophenyl)-N-methoxycarbonylmethyl- amide are subjected to Friedel-Crafts acylation with 3-(4-cyanophenyl)-propionic acid chloride
Yield: 540 mg (44% of theory)

e) 3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-sulfonic acid-N-(4-chlorophenyl)-N-methoxycarbonylmethyl-amide-hydrochloride

As in example 1g, 250 mg (0.46 mmol) 3-[3-(4-cyanophenyl)-propionyl]-1-methylindole-5-sulfonic acid-N-(4-chlorophenyl)-N-methoxycarbonylmethyl-amide are reacted with ethereal hydrochloric acid and then with ammonium carbonate.
Yield: 0.160 mg (58% of theory)
Melting point: 132-134°C
$C_{29}H_{29}ClN_4O_5S$ (581.10)
Mass spectrum: $(M+H)^+$ = 583, 581

Example 47

3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-sulfonic acid-N-(4-chlorophenyl)-N-hydroxycarbonylmethyl-amide-hydrochloride

Produced as in example 2 by saponification of 3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-sulfonic acid-N-(4-chlorophenyl)-N-methoxycarbonylmethyl-amide hydrochloride.
Yield: 78% of theory
Melting point: 236°C (decomp.)
$C_{27}H_{25}ClN_4O_5S$ (553.04)
Mass spectrum: $(M+H)^+$ = 555, 553

Example 48

3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-sulfonic acid-N-phenyl-N-hydroxycarbonylmethyl-amide-hydrochloride

---

0.11 g (0.18 mmol) 3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-5-sulfonic acid-N-(4-chlorophenyl)-N-hydroxycarbonylmethyl-amide hydrochloride are dissolved in 15 ml methanol and mixed with 0.11 g palladium/carbon (10%) and 0.3 ml (1.9 mmol) triethylamine. The reaction solution is hydrated in a Parr agitator for 5 hours at room temperature and at a hydrogen pressure of 3.4 bar. The catalyst is removed by filtration, 6.3 ml 1N hydrochloric acid are added, and the solvent is then removed *in vacuo*, followed by trituration with water and drying.
Yield: 60 mg (60% of theory)
$C_{27}H_{26}N_4O_5S$ (518.60)
Mass spectrum: $(M+H)^+ = 519$

Example 49

3-[3-(4-amidinophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-valeryl-1-methyl-5-indolamine hydrochloride

---

a) 1-methyl-5-nitroindole

56 g (0.50 mol) potassium-tert.butylate are added to a solution of 50 g (0.31 mol) 5-nitroindole in 500 ml DMF at room temperature. The solution is stirred for 30 minutes and then a solution of 37.7 ml (85 g, 0.60 mol) methyl iodide in 50 ml DMF is then added in drops at 5°C. The solution is stirred for 30 minutes at room temperature and heated for another 2 hours to 80°C. 14 g (0.12 mol) potassium-tert.butylate are then again added and 9.5 ml (0.15 mol) methyl iodide. After 20 hours of stirring at room temperature, the solvent is removed *in vacuo* and the residue is triturated with water. It is extracted with dichloromethane, dried over magnesium sulfate, concentrated to dryness and triturated with ether.
Yield: 50 g (92% of theory)
Melting point: 169°C

b) 3-[3-(4-cyanophenyl)-propionyl]-1-methyl-5-nitroindole

Produced as in example 1c by Friedel-Crafts acylation of 1-methyl-5-nitroindole with 3-(4-cyanophenyl)-propionic acid chloride.
Yield: 71% of theory
Melting point: 237°C

c) 3-[3-(4-cyanophenyl)-propionyl]-1-methyl-5-indolamine

Produced as in example 48 by catalytic hydration of 3-[3-(4-cyanophenyl)-propionyl]-1-methyl-5-nitroindole in DMF.

Yield: 95% of theory
Melting point: 228-230°C (decomp.)

d) 3-[3-(4-cyanophenyl)-propionyl]-N-ethoxycarbonylmethyl-1-methyl-5-indolamine

4.4 ml (3.2 g, 25 mmol) ethyldiisopropylamine and 2.3 ml (4.1 g, 19 mmol) iodoacetic acid ethylester are added to a solution of 5.0 g (16 mmol) 3-[3-4-cyanophenyl)-propionyl]-1-methyl-5-indolamine in 30 ml DMF. The solution is stirred overnight at 100°C, the solvent is removed *in vacuo* and the residue is chromatographed on silica gel (dichloromethane/ethyl acetate = 9:1). It is triturated after the solvent has been removed again with ether.
Yield: 5.9 g (92% of theory)
Melting point: 127°C

e) 3-[3-(4-cyanophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-valeryl-1-methyl-5-indolamine

0.22 ml (0.22 g, 1.9 mmol) valeryl chloride is added in drops to a solution of 0.70 g (1.8 mmol) 3-[3-(4-cyanophenyl)-propionyl]-N-ethoxycarbonylmethyl-1-methyl-5-indolamine and 0.55 ml (0.40 g, 4.0 mmol) triethylamine in 30 ml dichloromethane. The solution is heated to reflux for 4 hours. The solvent is then removed *in vacuo*, and the residue is chromatographed on silica gel (dichloromethane/ethyl acetate = 9:1) and triturated with ether after the solvent has been removed again.
Yield: 0.65 g (77% of theory)
Melting point: 130-132°C

f) 3-[3-(4-amidinophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-valeryl-1-methyl-5-indolamine hydrochloride

Produced as in example 1g by reaction of 3-[3-(4-cyanophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-valeryl-1-methyl-5-indolamine with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 75% of theory
Melting point: 132°C (decomp.)
$C_{28}H_{34}N_4O_4$ (490.61)
Mass spectrum: $(M+H)^{=}$ = 491

Example 50

3-[3-(4-amidinophenyl)-propionyl]-N-hydroxycarbonylmethyl-N-valeryl-1-methyl-5-indolamine hydrochloride

---

Produced as in example 2 by saponification of 3-[3-(4-amidinophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-valeryl-1-methyl-5-indolamine hydrochloride.
Yield: 70% of theory
Melting point: 226-228°C (decomp.)
$C_{26}H_{30}N_4O_4$ (462.55)

Mass spectrum: $(M+H)^{=}$ = 463

Example 51

3-[3-(4-amidinophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-cyclohexylcarbonyl-1-methyl-5-indolamine hydrochloride

---

Produced as in example 49 by reaction of 3-[3-(4-cyanophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-cyclohexylcarbonyl-1-methyl-5-indolamine with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 68% of theory
$C_{30}H_{36}N_4O_4$ (516.65)
Mass spectrum: $(M+H)^{=}$ = 517

Example 52

3-[3-(4-amidinophenyl)-propionyl]-N-hydroxycarbonylmethyl-N-cyclohexylcarbonyl-1-methyl-5-indolamine hydrochloride

---

Produced as in example 2 by saponification of 3-[3-(4-amidinophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-cyclohexylcarbonyl-1-methyl-5-indolamine hydrochloride.
Yield: 95% of theory
$C_{28}H_{32}N_4O_4$ (488.59)
Mass spectrum: $(M+H)^{=}$ = 489

Example 53

3-[3-(4-amidinophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-benzoyl-1-methyl-5-indolamine hydrochloride

---

Produced as in example 49 by reaction of 3-[3-(4-cyanophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-benzoyl-1-methyl-5-indolamine with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 60% of theory
Melting point: 164°C (decomp.)
$C_{30}H_{30}N_4O_4$ (510.60)
Mass spectrum: $(M+H)^{=}$ = 511

Example 54

3-[3-(4-amidinophenyl)-propionyl]-N-hydroxycarbonylmethyl-N-benzoyl-1-methyl-5-indolamine hydrochloride

---

Produced as in example 2 by saponification of 3-[3-(4-amidinophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-benzoyl-1-methyl-5-indolamine hydrochloride.
Yield: 98% of theory
Melting point: >280°C
$C_{28}H_{26}N_4O_4$ (482.54)
Mass spectrum: $(M+H)^{=}$ = 483

Example 55

3-[3-(4-amidinophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-(2-methoxyphenylcarbonyl)-1-methyl-5-indolamine hydrochloride

---

Produced as in example 49 by reaction of 3-[3-(4-cyanophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-(2-methoxyphenylcarbonyl)-1-methyl-5-indolamine with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 99% of theory
Melting point: 115°C (decomp.)
$C_{31}H_{32}N_4O_5$ (540.63)
Mass spectrum: $(M+H)^{=}$ = 541

Example 56

3-[3-(4-amidinophenyl)-propionyl]-N-hydroxycarbonylmethyl-N-(2-methoxyphenylcarbonyl)-1-methyl-5-indolamine hydrochloride

---

Produced as in example 2 by saponification of 3-[3-(4-amidinophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-(2-methoxyphenylcarbonyl)-1-methyl-5-indolamine hydrochloride.
Yield: 75% of theory
Melting point: 228°C (decomp.)
$C_{29}H_{28}N_4O_5$ (512.57)
Mass spectrum: $(M+H)^{=}$ = 513

Example 57

3-[3-(4-amidinophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-(2-naphthylcarbonyl)-1-methyl-5-indolamine hydrochloride

---

Produced as in example 49 by reaction of 3-[3-(4-cyanophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-(2-naphthylcarbonyl)-1-methyl-5-indolamine with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 71% of theory
Melting point: 172°C (decomp.)
$C_{34}H_{32}N_4O_4$ (560.65)
Mass spectrum: $(M+H)^{=}$ = 561

Example 58

3-[3-(4-amidinophenyl)-propionyl]-N-hydroxycarbonylmethyl-N-(2-naphthylcarbonyl)-1-methyl-5-indolamine hydrochloride

---

Produced as in example 2 by saponification of 3-[3-(4-amidinophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-(2-naphthylcarbonyl)-1-methyl-5-indolamine hydrochloride.
Yield: 84% of theory
Melting point: 236-238°C (decomp.)
$C_{32}H_{28}N_4O_4$ (532.60)
Mass spectrum: $(M+H)^{=}$ = 533

Example 59

3-[3-(4-amidinophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-(2-furoyl)-1-methyl-5-indolamine hydrochloride

---

Produced as in example 49 by reaction of 3-[3-(4-cyanophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-(2-furoyl)-1-methyl-5-indolamine with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 99% of theory
Melting point: 140°C (decomp.)
$C_{28}H_{28}N_4O_5$ (500.56)
Mass spectrum: $(M+H)^{=}$ = 501

Example 60

3-[3-(4-amidinophenyl)-propionyl]-N-hydroxycarbonylmethyl-N-(2-furoyl)-1-methyl-5-indolamine hydrochloride

---

Produced as in example 2 by saponification of 3-[3-(4-amidinophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-(2-furoyl)-1-methyl-5-indolamine hydrochloride.
Yield: 88% of theory
Melting point: >278°C
$C_{26}H_{24}N_4O_5$ (472.51)
Mass spectrum: $(M+H)^=$ = 473

Example 61

3-[3-(4-amidinophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-(2-pyridylcarbonyl)-1-methyl-5-indolamine hydrochloride

---

Produced as in example 49 by reaction of 3-[3-(4-cyanophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-(2-pyridylcarbonyl)-1-methyl-5-indolamine with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 91% of theory
Melting point: 120°C (decomp.)
$C_{29}H_{29}N_5O_4$ (511.59)
Mass spectrum: $(M+H)^=$ = 512

Example 62

3-[3-(4-amidinophenyl)-propionyl]-N-hydroxycarbonylmethyl-N-(2-pyridylcarbonyl)-1-methyl-5-indolamine hydrochloride

---

Produced as in example 2 by saponification of 3-[3-(4-amidinophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-(2-pyridylcarbonyl)-1-methyl-5-indolamine hydrochloride.

Yield: 88% of theory
Melting point: >275°C
$C_{27}H_{25}N_5O_4$ (483.53)
Mass spectrum: $(M+H)^=$ = 484

Example 63

3-[3-(4-amidinophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-(3-pyridylcarbonyl)-1-methyl-5-indolamine hydrochloride

---

Produced as in example 49 by reaction of 3-[3-(4-cyanophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-(3-pyridylcarbonyl)-1-methyl-5-indolamine with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 99% of theory
Melting point: 116°C (decomp.)
$C_{29}H_{29}N_5O_4$ (511.59)
Mass spectrum: $(M+H)^{=}$ = 512

Example 64

3-[3-(4-amidinophenyl)-propionyl]-N-hydroxycarbonylmethyl-N-(3-pyridylcarbonyl)-1-methyl-5-indolamine hydrochloride

---

Produced as in example 2 by saponification of 3-[3-(4-amidinophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-(3-pyridylcarbonyl)-1-methyl-5-indolamine hydrochloride.
Yield: 88% of theory
Melting point: 268°C (decomp.)
$C_{27}H_{25}N_5O_4$ (483.53)
Mass spectrum: $(M+H)^{=}$ = 484

Example 65

3-[3-(4-amidinophenyl)-propionyl]-N-(2-ethoxycarbonylethyl)-N-(3-pyridylcarbonyl)-1-methyl-5-indolamine hydrochloride

---

a) 3-[3-(4-cyanophenyl)-propionyl]-N-(2-ethoxycarbonylethyl)-1-methyl-5-indolamine

A solution of 2.0 g (6.0 mmol) 3-[3-(4-cyanophenyl)-propionyl]-1-methyl-5-indolamine (example 49c) and 0.76 ml (0.7 g, 7.0 mmol) acrylic acid ethylester in 15 ml glacial acetic acid are heated to reflux for 6 hours. The solvent is then removed *in vacuo* and the residue is divided between dichloromethane and water. The organic phase is dried over sodium sulfate, freed of the solvent *in vacuo* and chromatographed on silica gel (dichloromethane/ethyl acetate = 17:3).
Yield: 0.5 g (19% of theory)

b) 3-[3-(4-cyanophenyl)-propionyl]-N-(2-ethoxycarbonylethyl)-N-(3-pyridylcarbonyl)-1-methyl-5-indolamine

Produced as in example 49e from 3-[3-(4-cyanophenyl)-propionyl]-N-(2-ethoxycarbonylethyl)-1-methyl-5-indolamine and nicotinic acid chloride.

Yield: 88% of theory (foamy product).

c) 3-[3-(4-amidinophenyl)-propionyl]-N-(2-ethoxycarbonylethyl)-N-(3-pyridylcarbonyl)-1-methyl-5-indolamine hydrochloride

Produced as in example 1g by reaction of 3-[3-(4-cyanophenyl)-propionyl]-N-(2-ethoxycarbonylethyl)-N-(3-pyridylcarbonyl)-1-methyl-5-indolamine with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 91% of theory
Melting point: 120°C (decomp.)
$C_{30}H_{31}N_5O_4$ (525.61)
Mass spectrum: $(M+H)^+ = 526$

Example 66

3-[3-(4-amidinophenyl)-propionyl]-N-(2-hydroxycarbonylethyl)-N-(3-pyridinylcarbonyl)-1-methyl-5-indolamine hydrochloride

---

Produced as in example 2 by saponification of 3-[3-(4-amidinophenyl)-propionyl]-N-(2-ethoxycarbonlyethyl)-N-(3-pyridylcarbonyl)-1-methyl-5-indolamine hydrochloride
Yield: 88% of theory
Melting point: 200°C (decomp.)
$C_{28}H_{27}N_5O_4$ (497.56)
Mass spectrum: $(M+H)^+ = 498$

Example 67

3-[3-(4-amidinophenyl)-propionyl]-N-ethoxycarbonylmethyl)-N-(4-thiazolylcarbonyl)-1-methyl-5-indolamine hydrochloride

---

Produced as in example 49 by reaction of 3-[3-(4-cyanophenyl)-propionyl]-N-ethoxycarbonlymethyl)-N-(4-thiazolylcarbonyl)-1-methyl-5-indolamine with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 83% of theory
Melting point: 160°C (decomp.)
$C_{27}H_{27}N_5O_4S$ (517.61)
Mass spectrum: $(M+H)^+ = 518$

Example 68

3-[3-(4-amidinophenyl)-propionyl]-N-hydroxycarbonylmethyl)-N-(4-thiazolylcarbonyl)-1-methyl-5-indolamine hydrochloride

---

Produced as in example 2 by saponification of 3-[3-(4-amidinophenyl)-propionyl]-N-ethoxycarbonlymethyl)-N-(4-thiazolylcarbonyl)-1-methyl-5-indolamine hydrochloride.
Yield: 92% of theory
Melting point: >280°C
$C_{25}H_{23}N_5O_4S$ (489.56)
Mass spectrum: $(M+H)^+ = 490$

Example 69

3-[3-(4-amidinophenyl)-propionyl]-N-ethoxycarbonylmethyl)-N-(8-quinolinylcarbonyl)-1-methyl-5-indolamine hydrochloride

---

Produced as in example 49 by reaction of 3-[3-(4-cyanophenyl)-propionyl]-N-ethoxycarbonlymethyl)-N-(8-quinolinylcarbonyl)-1-methyl-5-indolamine with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 91% of theory
Melting point: 150°C (decomp.)
$C_{33}H_{31}N_5O_4$ (561.65)
Mass spectrum: $(M+H)^+ = 562$

Example 70

3-[3-(4-amidinophenyl)-propionyl]-N-hydroxycarbonylmethyl)-N-(8-quinolinylcarbonyl)-1-methyl-5-indolamine hydrochloride

---

Produced as in example 2 by saponification of 3-[3-(4-amidinophenyl)-propionyl]-N-ethoxycarbonylmethyl)-N-(8-quinolinylcarbonyl)-1-methyl-5-indolamine hydrochloride.
Yield: 84% of theory
Melting point: 170°C (decomp.)
$C_{31}H_{27}N_5O_4$ (533.59)
Mass spectrum: $(M+H)^+ = 534$

Example 71

3-[3-(4-amidinophenyl)-propionyl]-N-methoxycarbonymethylaminocarbonyl-methyl)-N-(8-quinolinylcarbonyl)-1-methyl-5-indolamine dyhydroiodide

---

Produced as in examples 49 and 21 by reaction of 3-[3-(4-cyanophenyl)-propionyl]-N-methoxycarbonylmethylaminocarbonylmethyl)-N-(8-quinolinylcarbonyl)-1-methyl-5-indolamine with hydrogen sulfide, methyliodide and ammonium acetate.
Yield: 82% of theory
Melting point: 115°C (decomp.)
$C_{34}H_{32}N_6O_5$ (604.67)
Mass spectrum: $(M+H)^+ = 605$

Example 72

3-[3-(4-amidinophenyl)-propionyl]-N-hydroxycarbonymethylaminocarbonyl-methyl)-N-(8-quinolinylcarbonyl)-1-methyl-5-indolamine dyhydroiodide

---

A solution of 0.4 g (0.5 mmol) 3-[3-(4-amidinophenyl)-propionyl]-N-methoxycarbonylmethylaminocarbonylmethyl)-N-(8-quinolinylcarbonyl)-1-methyl-5-indolamine dihydroiodide in 5 ml methanol and 5 ml dioxane is mixed with 3.2 1N caustic soda solution and stirred for 30 minutes at room temperature. The solvent is then removed *in vacuo*, and the residue is dried *in vacuo* over potassium hydroxide and triturated with ethanol and dichloromethane.
Yield: 0.33 g (96% of theory)
Melting point: 90°C (decomp.)
$C_{33}H_{30}N_6O_5$ (590.64)
Mass spectrum: $(M+H)^+ = 591$

Example 73

1-{3-[3-(4-amidinophenyl)-propionyl]-1-methyl-5-indolyl}-3-phenyl-imidazolidine-2,4-dione hydrochloride

---

a) 3-[3-(4-cyanophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-phenylaminocarbonyl-1-methyl-5-indolamine

A solution of 0.90 g (2.3 mmol) 3-[3-(4-cyanophenyl)-propionyl]-N-ethoxycarbonylmethyl-1-methyl-5-indolamine (example 49d) and 0.26 ml (0.29 g, 2.4 mmol) phenylisocyanate in 30 ml dichloromethane is heated overnight to reflux. 0.15 ml (1.4 mmol) phenylisocyanate is again added and the solution is heated for another 3 hours to reflux. The solvent is then removed *in vacuo* and the residue is chromatographed on silica gel (toluene/ethyl acetate = 7:3).
Yield: 0.80 g (68% of theory)
Melting point: 78°C

b) 1-{3-[3-(4-amidinophenyl)-propionyl]-1-methyl-5-indolyl}-3-phenyl-imidazolidine-2,4-dione hydrochloride

Produced as in example 1g by reaction of 3-[3-(4-cyanophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-phenylaminocarbonyl-1-methyl-5-indolamine with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 62% of theory
Melting point: 210°C (decomp.)
$C_{28}H_{25}N_5O_3$ (479.54)
Mass spectrum: $(M+H)^+ = 480$

Example 74

3-{3-(4-amidinophenyl)-propionyl]-N-hydroxycarbonylmethyl-N-phenylaminocarbonyl-1-methyl-5-indolamine hydrochloride

---

Produced as in example 2 by saponification of 1-{3-[3-(4-amidinophenyl)-propionyl]-1-methyl-5-indolyl}-3-phenyl-imidazolidine-2,4-dione hydrochloride.
Yield: 90% of theory
Melting point: 190°C (decomp.)
$C_{28}H_{27}N_5O_4$ (497.56)
Mass spectrum: $(M+H)^+ = 498$

Example 75

3-[3-(4-amidinophenyl)-propionyl]-N-butylsulfonyl-1-methyl-5-indolamine hydrochloride

---

a) 3-[3-(4-cyanophenyl)-propionyl]-N-butylsulfonyl-1-methyl-5-indolamine

0.9 g (5.8 mmol) butane sulfonic acid chloride are added in portions to a solution of 1.7 g (5.6 mmol) 3-[3-(4-cyanophenyl)-propionyl]-1-methyl-5-indolamine (example 49c) in 50 ml pyridine at room temperature. The solution is then heated for 1 hour to 110°C. The solvent is removed *in vacuo* and the residue obtained is mixed with dilute hydrochloric acid and immediately extracted with dichloromethane. The combined organic phases are dried over sodium sulfate, freed of the solvent *in vacuo* and the residue obtained is triturated with ether.
Yield: 2.0 g (84% of theory)
Melting point: 184°C
$C_{23}H_{25}N_3O_3S$ (423.53)
Calculated: C 65.22 H 5.94 N 9.92
Found: C 64.95 H 6.06 N 9.79

b) 3-[3-(4-amidinophenyl)-propionyl]-N-butylsulfonyl-1-methyl-5-indolamine hydrochloride

Produced as in example 1g by reaction of 3-[3-(4-cyanophenyl)-propionyl]-N-butylsulfonyl-1-methyl-5-indolamine with ethanolic hydrochloric acid and ammmonium carbonate.

Yield: 48% of theory
Melting point: 80°C (decomp.)
$C_{23}H_{28}N_4O_3S$ (440.57)
Mass spectrum: $(M+H)^+ = 441$

Example 76

3-[3-(4-amidinophenyl)-propionyl]-N-butylsulfonyl-N-ethoxycarbonylmethyl-1-methyl-5-indolamine hydrochloride

---

a) 3-[3-(4-cyanophenyl)-propionyl]-N-butylsulfonyl-N-ethoxycarbonylmethyl-1-methyl-5-indolamine

0.39 g (3.5 mmol) potassium-tert.butylate are added to a solution of 1.4 g (3.3 mmol) 3-[3-(4-cyanophenyl)-propionyl]-N-butylsulfonyl-1-methyl-5-indolamine (example 75a) in 25 ml DMF at room temperature and stirred for 1 hour. 0.39 ml (0.59 g, 3.5 mmol) bromoacetic acid ethylester are then added in drops and stirred at room temperature overnight. The solvent is removed *in vacuo* and the residue is chromatographed on silica gel (dichloromethane/ethyl acetate = 9:1).
Yield: 1.3 g (77% of theory)
Melting point: 144°C
$C_{27}H_{31}N_3O_5S$ (509.63)
Calculated: C 63.63 H 6.13 N 8.24
Found: C 63.53 H 6.25 N 8.05

b) 3-[3-(4-amidinophenyl)-propionyl]-N-butylsulfonyl-N-ethoxycarbonylmethyl-1-methyl-5-indolamine hydrochloride

Produced as in example 1g by reaction of 3-[3-(4-cyanophenyl)-propionyl]-N-butylsulfonyl-N-ethoxycarbonylmethyl-1-methyl-5-indolamine with ethanolic hydrochloric acid and ammmonium carbonate.
Yield: 63% of theory
Melting point: 150°C (decomp.)
$C_{27}H_{34}N_4O_5S$ (526.66)
Mass spectrum: $(M+H)^+ = 527$

Example 77

3-[3-(4-amidinophenyl)-propionyl]-N-butylsulfonyl-N-hydroxycarbonylmethyl-1-methyl-5-indolamine hydrochloride

---

Produced as in example 2 by saponification of 3-[3-(4-amidinophenyl)-propionyl]-N-butylsulfonyl-N-ethoxycarbonylmethyl-1-methyl-5-indolamine hydrochloride.
Yield: 99% of theory
Melting point: 186-188°C
$C_{25}H_{30}N_4O_5S$ (498.61)
Mass spectrum: $(M+H)^+ = 499$
$C_{25}H_{30}N_4O_5S \times HCl$ (535.07)
Calculated: C 56.11 H 5.83 N 10.47
Found: C 56.33 H 5.97 N 10.44

Example 78

3-[3-(4-amidinophenyl)-propionyl]-N-benzylsulfonyl-1-methyl-5-indolamine hydrochloride

Produced as in example 75 by reaction of 3-[3-(4-cyanophenyl)-propionyl]-N-benzylsulfonyl-1-methyl-5-indolamine with ethanolic hydrochloric acid and ammmonium carbonate.
Yield: 30% of theory
Melting point: >120°C (decomp.)
$C_{26}H_{26}N_4O_3S$ (474.59)
Mass spectrum: $(M+H)^+ = 475$

Example 79

3-[3-(4-amidinophenyl)-propionyl]-N-benzylsulfonyl-N-ethoxycarbonylmethyl-1-methyl-5-indolamine hydroiodide

---

Produced as in examples 76 and 21 from 3-[3-(4-cyanophenyl)-propionyl]-N-benzylsulfonyl-N-ethoxycarbonylmethyl-1-methyl-5-indolamine with hydrogen sulfide, methyliodide and ammonium acetate.
Yield: 51% of theory
Melting point: 226°C (decomp.)
$C_{30}H_{32}N_4O_5S$ (560.68)
Mass spectrum: $(M+H)^+ = 561$

Example 80

3-[3-(4-amidinophenyl)-propionyl]-N-benzylsulfonyl-N-hydroxycarbonylmethyl-1-methyl-5-indolamine hydrochloride

---

Produced as in example 2 by saponification of 3-[3-(4-amidinophenyl)-propionyl]-N-benzylsulfonyl-N-ethoxycarbonylmethyl-1-methyl-5-indolamine hydroiodide.
Yield: 97% of theory
Melting point: 277°C (decomp.)
$C_{28}H_{28}N_4O_5S$ (532.62)
Mass spectrum: $(M+H)^+ = 533$

Example 81

3-[3-(4-amidinophenyl)-propionyl]-N-phenylsulfonyl-1-methyl-5-indolamine hydrochloride

---

Produced as in example 75 by reaction of 3-[3-(4-cyanophenyl)-propionyl]-N-phenylsulfonyl-1-methyl-5-indolamine with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 80% of theory
Melting point: >275°C
$C_{25}H_{24}N_4O_3S$ (460.56)
Mass spectrum: $(M+H)^+ = 461$

Example 82

3-[3-(4-amidinophenyl)-propionyl]-N-phenylsulfonyl-N-ethoxycarbonylmethyl-1-methyl-5-indolamine hydrochloride

---

Produced as in example 76 by reaction of 3-[3-(4-cyanophenyl)-propionyl]-N-phenylsulfonyl-N-ethoxycarbonylmethyl-1-methyl-5-indolamine with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 78% of theory
Melting point: 110°C (decomp.)
$C_{29}H_{30}N_4O_5S$ (546.65)
Mass spectrum: $(M+H)^+ = 547$

Example 83

3-[3-(4-amidinophenyl)-propionyl]-N-phenylsulfonyl-N-hydroxycarbonylmethyl-1-methyl-5-indolamine hydrochloride

---

Produced as in example 2 by saponification of 3-[3-(4-amidinophenyl)-propionyl]-N-phenylsulfonyl-N-ethoxycarbonylmethyl-1-methyl-5-indolamine hydrochloride.
Yield: 95% of theory
Melting point: 276-278°C (decomp.)
$C_{27}H_{26}N_4O_5S$ (518.60)
Mass spectrum: $(M+H)^+ = 519$

Example 84

3-[3-(4-amidinophenyl)-propionyl]-N-[5-chloro-2-(methoxycarbonylmethyloxy)-phenylsulfonyl]-1-methyl-5-indolamine hydroiodide

---

a) 5-chloro-2-(methoxycarbonylmethyloxy)-phenylsulfonic acid chloride

1 g (5.0 mmol) 4-chlorophenoxy acetic acid ethylester is added to 3.3 ml (5.8 g, 50 mmol) chlorosulfonic acid in portions with stirring at room temperature. The mixture is then heated for 10 minutes to 70°C. It is then poured onto ice and extracted with dichloromethane, the solvent being dried and removed *in vacuo*.
Yield: 1.3 g (87% of theory); oily product which crystallizes when triturated).

b) N-[5-chloro-2-(methoxycarbonylmethyloxy)-phenylsulfonyl]-3-[3-(4-cyanophenyl)-propionyl]-1-methyl-5-indolamine hydrochloride

Produced as in example 75a from 3-[3-(4-cyanophenyl)-propionyl]-1-methyl-5-indolamine and 5-chloro-2-(methoxycarbonylmethyloxy)-benzene sulfonic acid chloride.
Yield: 66% of theory
Melting point: 224-225°C

c) 3-[3-(4-amidinophenyl)-propionyl]-N-[5-chloro-2-(methoxycarbonylmethyloxy)-phenylsulfonyl]-1-methyl-5-indolamine hydroiodide

Produced as in example 79 from 3-[3-(4-cyanophenyl)-propionyl]-N-[5-chloro-2-(methoxycarbonylmethyloxy)-phenylsulfonyl]-1-methyl-5-indolamine with hydrogen sulfide, methyliodide and ammonium acetate.
Yield: 48% of theory
Melting point: 180°C (decomp.)
$C_{28}H_{27}ClN_4O_6S$ (583.07)
Mass spectrum: $(M+H)^+ = 585, 583$

Example 85

3-[3-(4-amidinophenyl)-propionyl]-N-[5-chloro-2-(methoxycarbonylmethyloxy)-phenylsulfonyl]-1-methyl-5-indolamine hydrochloride

---

Produced as in example 2 by saponification of 3-[3-(4-amidinophenyl)-propionyl]-N-[5-chloro-2-(methoxycarbonylmethyloxy)-phenylsulfonyl]-1-methyl-5-indolamine hydroiodide.
Yield: 88% of theory
Melting point: 200°C (decomp.)
$C_{27}H_{25}ClN_4O_6S$ (569.04)
Mass spectrum: $(M+H)^+$ = 571, 569

Example 86

3-[3-(4-amidinophenyl)-propionyl]-N-(2.5-dichlorophenylsulfonyl)-1-methyl-5-indolamine hydrochloride

---

Produced as in example 75 by reaction of 3-[3-(4-cyanophenyl)-propionyl]-N-(2.5-dichlorophenylsulfonyl)-1-methyl-5-indolamine with ethanolic hydrochloric acid and ammonium carbonate
Yield: 48% of theory
Melting point: 244°C (decomp.)
$C_{25}H_{22}Cl_2N_4O_3S$ (529.45)
Mass spectrum: $(M+H)^+$ = 533, 531, 529

Example 87

3-[3-(4-amidinophenyl)-propionyl]-N-(2.5-dichlorophenylsulfonyl)-N-ethoxycarbonylmethyl-1-methyl-5-indolamine hydroiodide

---

Produced as in example 79 from 3-[3-(4-cyanophenyl)-propionyl]-N-(2.5-dichlorophenylsulfonyl)-N-ethoxycarbonylmethyl-1-methyl-5-indolamine with hydrogen sulfide, methyliodide and ammonium acetate.
Yield: 58% of theory
Melting point: 130°C (decomp.)
$C_{29}H_{28}Cl_2N_4O_3S$ (615.54)
Mass spectrum: $(M+H)^+$ = 619, 617, 615

Example 88

3-[3-(4-amidinophenyl)-propionyl]-N-(2.5-dichlorophenylsulfonyl)-N-hydroxycarbonylmethyl-1-methyl-5-indolamine hydrochloride

---

Produced as in example 2 by saponification of 3-[3-(4-amidinophenyl)-propionyl]-N-(2.5-dichlorophenylsulfonyl)-N-ethoxycarbonylmethyl-1-methyl-5-indolamine hydroiodide.
Yield: 95% of theory
Melting point: >272°C
$C_{27}H_{24}Cl_2N_4O_5S$ (587.49)
Mass spectrum: $(M+H)^+$ = 591, 589, 587

Example 89

3-[3-(4-amidinophenyl)-propionyl]-N-(4-amino-3,5-dichlorophenylsulfonyl)-1-methyl-5-indolamine hydrochloride

---

Produced as in example 75 by reaction of 3-[3-(4-cyanophenyl)-propionyl]-N-(4-amino-3,5-dichlorophenylsulfonyl)-1-methyl-5-indolamine with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 46% of theory
Melting point: 192°C (decomp.)
$C_{25}H_{23}Cl_2N_5O_3S$ (544.47)
Mass spectrum: $(M+H)^+$ = 548, 546, 544

Example 90

3-[3-(4-amidinophenyl)-propionyl]-N-(4-amino-3,5-dichlorophenylsulfonyl)-N-ethoxycarbonylmethyl-1-methyl-5-indolamine hydroiodide

---

Produced as in example 79 from 3-[3-(4-cyanophenyl)-propionyl]-N-(4-amino-3,5-dichlorophenylsulfonyl)-N-ethoxycarbonylmethyl-1-methyl-5-indolamine with hydrogen sulfide, methyliodide and ammonium acetate.
Yield: 52% of theory
Melting point: 220°C (decomp.)
$C_{29}H_{29}Cl_2N_5O_5S$ (630.56)
Mass spectrum: $(M+H)^+$ = 634, 632, 630

Example 91

3-[3-(4-amidinophenyl)-propionyl]-N-(4-amino-3,5-dichlorophenylsulfonyl)-N-hydroxycarbonylmethyl-1-methyl-5-indolamine hydrochloride

---

Produced as in example 2 by saponification of 3-[3-(4-amidinophenyl)-propionyl]-N-(4-amino-3,5-dichlorophenylsulfonyl)-N-ethoxycarbonylmethyl-1-methyl-5-indolamine hydroiodide.
Yield: 74% of theory
Melting point: >270°C
$C_{27}H_{25}Cl_2N_5O_5S$ (602.50)
Mass spectrum: $(M+H)^+$ = 606, 604, 602

Example 92

3-[3-(4-amidinophenyl)-propionyl]-N-ethoxycarbonylmethyl-1-methyl-5-indolamine hydrochloride

---

Produced as in example 76 by reaction of of 3-[3-(4-cyanophenyl)-propionyl]-N-(4-amino-3,5-dichlorophenylsulfonyl)-N-ethoxycarbonylmethyl-1-methyl-5-indolamine with ethanolic hydrochloric acid and ammonium carbonate with sulfonamide cleavage.
Yield: 50% of theory
Melting point: 120°C (decomp.)
$C_{23}H_{26}N_4O_3$ (406.49)
Mass spectrum: $(M+H)^+$ = 407

Example 93

3-[3-(4-amidinophenyl)-propionyl]-N-hydroxycarbonylmethyl-1-methyl-5-indolamine hydrochloride

---

Produced as in example 2 by saponification of 3-[3-(4-amidinophenyl)-propionyl]-N-ethoxycarbonylmethyl-1-methyl-5-indolamine hydrochloride.
Yield: 78% of theory
Melting point: 188°C (decomp.)
$C_{21}H_{22}N_4O_3$ (378.44)
Mass spectrum: $(M+H)^+$ = 379

Example 94

3-[3-(4-amidinophenyl)-propionyl]-N-(2,4,6-trimethylphenylsulfonyl)-1-methyl-5-indolamine hydroiodide

---

Produced as in example 79 from 3-[3-(4-cyanophenyl)-propionyl]-N-(2,4,6-trimethylphenylsulfonyl)-1-methyl-5-indolamine with hydrogen sulfide, methyliodide and ammonium acetate.
Yield: 63% of theory
Melting point: 128°C (decomp.)
$C_{28}H_{30}N_4O_3S$ (502.64)
Mass spectrum: $(M+H)^+ = 503$

Example 95

3-[3-(4-amidinophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-(2,4,6-trimethylphenylsulfonyl)-1-methyl-5-indolamine hydroiodide

---

Produced as in example 79 from 3-[3-(4-cyanophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-(2,4,6-trimethylphenylsulfonyl)-1-methyl-5-indolamine with hydrogen sulfide, methyliodide and ammonium acetate.
Yield: 40% of theory
Melting point: 100°C (decomp.)
$C_{32}H_{36}N_4O_5S$ (588.73)
Mass spectrum: $(M+H)^+ = 589$

Example 96

3-[3-(4-amidinophenyl)-propionyl]-N-hydroxycarbonylmethyl-N-(2,4,6-trimethylphenylsulfony)-1-methyl-5-indolamine hydrochloride

---

Produced as in example 2 by saponification of 3-[3-(4-amidinophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-(2,4,6-trimethylphenylsulfonyl)-1-methyl-5-indolamine hydroiodide.
Yield: 72% of theory
Melting point: >270°C
$C_{30}H_{32}N_4O_5S$ (560.68)
Mass spectrum: $(M+H)^+ = 561$

Example 97

3-[3-(4-amidinophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-(1-naphthylsulfonyl)-1-methyl-5-indolamine hydroiodide

---

Produced as in example 79 from 3-[3-(4-cyanophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-(1-naphthylsulfonyl)-1-methyl-5-indolamine with hydrogen sulfide, methyliodide and ammonium acetate.
Yield: 61% of theory
Melting point: 230°C (decomp.)
$C_{33}H_{32}N_4O_5S$ (596.71)
Mass spectrum: $(M+H)^+ = 597$

Example 98

3-[3-(4-amidinophenyl)-propionyl]-N-hydroxycarbonylmethyl-N-(1-naphthylsulfonyl)-1-methyl-5-indolamine hydrochloride

---

Produced as in example 2 by saponification of 3-[3-(4-amidinophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-(naphthylsulfonyl)-1-methyl-5-indolamine hydroiodide.
Yield: 99% of theory
Melting point: >275°C
$C_{31}H_{28}N_4O_5S$ (568.66)
Mass spectrum: $(M+H)^+ = 569$

Example 99

3-[3-(4-amidinophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-(2-pyridylsulfonyl)-1-methyl-5-indolamine hydrochloride

---

Produced as in example 76 by reaction of 3-[3-(4-cyanophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-(2-pyridylsulfonyl)-1-methyl-5-indolamine with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 80% of theory
Melting point: 233°C (decomp.)
$C_{28}H_{29}N_5O_5S$ (547.64)
Mass spectrum: $(M+H)^+ = 548$

Example 100

3-[3-(4-amidinophenyl)-propionyl]-N-hydroxycarbonylmethyl-N-(2-pyridylsulfonyl) 1-methyl-5-indolamine hydrochloride

---

Produced as in example 2 by saponification of 3-[3-(4-amidinophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-(2-pyridylsulfonyl)-1-methyl-5-indolamine hydrochloride.
Yield: 82% of theory
Melting point: 232°C (decomp.)
$C_{26}H_{25}N_5O_5S$ (519.58)
Mass spectrum: $(M+H)^+ = 520$

Example 101

3-[3-(4-amidinophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-(5-isoquinolinylsulfonyl)-1-methyl-5-indolamine hydrochloride

---

Produced as in example 76 by reaction of 3-[3-(4-cyanophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-(5-isoquinolinylsulfonyl)-1-methyl-5-indolamine with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 99% of theory
Melting point: 200°C (decomp.)
$C_{32}H_{31}N_5O_5S$ (597.70)
Mass spectrum: $(M+H)^+ = 598$

Example 102

3-[3-(4-amidinophenyl)-propionyl]-N-hydroxycarbonylmethyl-N-(5-isoquinolinylsulfonyl) 1-methyl-5-indolamine hydrochloride

---

Produced as in example 2 by saponification of 3-[3-(4-amidinophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-(5-isoquinolinylsulfonyl)-1-methyl-5-indolamine hydrochloride.
Yield: 73% of theory
Melting point: 232°C (decomp.)
$C_{30}H_{27}N_5O_5S$ (569.64)
Mass spectrum: $(M+H)^+ = 570$

Example 103

3-[3-(4-amidinophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-(4-benzothiazolylsulfonyl)-1-methyl-5-indolamine hydrochloride

---

Produced as in example 76 by reaction of 3-[3-(4-cyanophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-(4-benzothiazolylsulfonyl)-1-methyl-5-indolamine with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 92% of theory
Melting point: 175°C (decomp.)
$C_{30}H_{29}N_5O_5S_2$ (603.72)
Mass spectrum: $(M+H)^+ = 604$

Example 104

3-[3-(4-amidinophenyl)-propionyl]-N-hydroxycarbonylmethyl-N-(4-benzothiazolylsulfonyl) 1-methyl-5-indolamine hydrochloride

---

Produced as in example 2 by saponification of 3-[3-(4-amidinophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-(4-benzothiazolylsulfonyl)-1-methyl-5-indolamine hydrochloride.
Yield: 84% of theory
Melting point: 240°C (decomp.)
$C_{28}H_{25}N_5O_5S_2$ (575.67)
Mass spectrum: $(M+H)^+ = 576$

Example 105

3-[3-(4-amidinophenyl)-propionyl]-N-(8-quinolinylsulfinyl)-1-methyl-5-indolamine

---

Produced as in example 75 by reaction of 3-[3-(4-cyanophenyl)-propionyl]-N-(8 quinolinylsulfonyl)-1-methyl-5-indolamine with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 54% of theory
Melting point: 191°C (decomp.)
$C_{28}H_{25}N_5O_3S$ (511.61)
Mass spectrum: $(M+H)^+ = 512$

Example 106

3-[3-(4-amidinophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-(8-quinolinylsulfinyl)-1-methyl-5-indolamine

---

Produced as in example 76 by reaction of 3-[3-(4-cyanophenyl)-propionyl]-N-ethoxycarbonylmethyl-(8 quinolinylsulfonyl)-1-methyl-5-indolamine with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 42% of theory
Melting point: 92°C (decomp.)
$C_{32}H_{31}N_5O_5S$ (597.70)
Mass spectrum: $(M+H)^+$ = 598

Example 107

3-[3-(4-amidinophenyl)-propionyl]-N-hydroxycarbonylmethyl-N-(8-quinolinlylsulfonyl) 1-methyl-5-indolamine hydrochloride

---

Produced as in example 2 by saponification of 3-[3-(4-amidinophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-(8-quinolinylsulfonyl)-1-methyl-5-indolamine.
Yield: 98% of theory
Melting point: 132°C (decomp.)
$C_{30}H_{27}N_5O_5S$ (569.64)
Mass spectrum: $(M+H)^+$ = 570

Example 108

3-{3-[4-(N-methoxycarbonyl)-amidinophenyl]-propionyl}-N-ethoxycarbonylmethyl-N-(8-quinolinylsulfonyl)-1-methyl-5-indolamine

---

0.07 ml (87 mg, 0.92 mmol) chloroformic acid ethylester is added in drops at room temperature to a solution of 0.50 g (0.79 mmol) 3-[3-(4-amidinophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-(8-quinolinylsulfonyl)-1-methyl-5-indolamine (example 106) and 0.19 g (1.75 mmol) sodium carbonate in 10 ml THF and 10 ml water. The mixture is stirred for 24 hours and filtered off from the insoluble part. The filtrate is dried over sodium sulfate, freed of the solvent *in vacuo* and filtered over silica gel (ethyl acetate).
Yield: 0.45 g (87% of theory)
Melting point: 100°C (decomp.)
$C_{34}H_{33}N_5O_7S$ (655.74)
Mass spectrum: $(M+H)^+$ = 656

Example 109

3-{3-[4-(N-benzyloxycarbonyl)-amidinophenyl]-propionyl}-N-ethoxycarbonylmethyl-N-(8-quinolinylsulfonyl)-1-methyl-5-indolamine

---

Produced as in example 108 from 3-{3-[4-amidinophenyl]-propionyl]-N-ethoxycarbonylmethyl-N-(8-quinolinylsulfonyl)-1-methyl-5-indolamine (example 106) and chloroformic acid benzylester.
Yield: 78% of theory
Melting point: 112°C (decomp.)
$C_{40}H_{37}N_5O_7S$ (731.83)
Mass spectrum: $(M+H)^+ = 732$

Example 110

3-[3-(4-amidinophenyl)-propionyl}-N-ethoxycarbonylmethylaminocarbonylmethyl-N-(8-quinolinylsulfonyl)-1-methyl-5-indolamine hydroiodide

---

a) 3-[3-(4-cyanophenyl)-propionyl]-N-ethoxycarbonylmethylaminocarbonyl-methyl-N-(8-quinolinylsulfonyl)-1-methyl-5-indolamine

0.25 g (1.4 mmol) CDI is added to a solution of 0.55 g (1.0 mmol) 3-[3-(4-cyanophenyl)-propionyl]-N-hydroxycarbonylmethyl-N-(8-quinolinylsulfonyl)-1-methyl-5-indolamine in 20 ml DMF and stirred for 30 minutes at 40°C. A solution of 0.15 g (1.1 mmol) glycine ethylester hydrochloride and 0.17 ml (0.12 g, 1.2 mmol) triethylamine in 5 ml DMF is then added and the mixture is heated for 20 hours to 60°C. The solvent is then removed *in vacuo* and the residue is divided between dichlormethane and ice water with a little 1N caustic soda solution. The organic phase is dried over sodium sulfate and freed of the solvent *in vacuo*. The residue thus obtained is chromatographed on silica gel (dichloromethane/ethyl acetate = 9:1).
Yield: 0.45 g (71% of theory; oily product).

b) 3-[3-(4-amidinophenyl)-propionyl]-N-ethoxycarbonylmethylaminocarbonyl-methyl-N-(8-quinolinylsulfonyl)-1-methyl-5-indolamine hydroiodide

Produced as in example 79 from 3-[3-(4-cyanophenyl)-propionyl]-N-ethoxycarbonylmethylaminocarbonylmethyl-N-(8-quinolinylsulfonyl)-1-methyl-5-indolamine with hydrogen sulfide, methyliodide and ammonium acetate.
Yield: 61% of theory
Melting point: 110°C (decomp.)
$C_{34}H_{34}N_6O_6S$ (654.75)
Mass spectrum: $(M+H)^+ = 655$

Example 111

3-[3-(4-amidinophenyl)-propionyl]-N-hydroxycarbonylmethylaminocarbonyl-methyl-N-(8-quinolinylsulfonyl)-1-methyl-5-indolamine hydroiodide

---

Produced as in example 2 by saponification of 3-[3-(4-amidinophenyl)-propionyl]-N-ethoxycarbonylmethylaminocarbonylmethyl-N-(8-quinolinylsulfonyl)-1-methyl-5-indolamine hydroiodide.
Yield: 83% of theory
Melting point: 215°C (decomp.)
$C_{32}H_{30}N_6O_6S$ (626.70)
Mass spectrum: $(M+H)^+ = 627$

Example 112

3-{3-[4-(N-methoxycarbonyl)-amidinophenyl]-propionyl}-N-methoxycarbonylmethylaminocarbonylmethyl-N-(8-quinolinylsulfonyl)-1-methyl-5-indolamine

---

Produced as in example 108 from 3-[3-(4-amidinophenyl)-propionyl]-N-methoxycarbonylmethylaminocarbonylmethyl-N-(8-quinolinylsulfonyl)-1-methyl-5-indolamine hydroiodide and chloroformic acid methylester.
Yield: 29% of theory
$C_{35}H_{34}N_6O_8S$ (698.76)
Mass spectrum: $(M+H)^+ = 699$

Example 113

3-[3-(4-amidinophenyl)-propionyl]-N-[bis-(methoxycarbonylmethyl)-aminocarbonylmethyl]-N-(8-quinolinylsulfonyl)-1-methyl-5-indolamine hydroacetate

---

a) Bromoacetic acid-N,N-bis-(methoxycarbonylmethyl)-amide

1 ml (1.9 g, 12 mmol) bromoacetic acid chloride is added in drops at room temperature to a solution of 2.0 g (10 mmol) iminodiacetic acid dimethylester hydrochloride and 2 ml (1.5 g, 15 mmol) triethylamine in 40 ml dichloromethane. The solution is poured onto ice water, acidified with dilute hydrochloric acid and extracted with dichloromethane. The organic phase is dried over sodium sulfate and concentrated by evaporation. The residue is chromatographed on silica gel (dichloromethane/ethyl acetate = 9:1).
Yield: 1.4 g (50% of theory; pale yellow oil).

b) 3-[3-(4-cyanophenyl)-propionyl]-N-[bis-(methoxycarbonylmethyl)-aminocarbonylmethyl]-N-(8-quinolinylsulfonyl)-1-methyl-5-indolamine

Produced as an oily product as in example 76a from 3-[3-(4-cyanophenyl)-propionyl]-N-(8-quinolinylsulfonyl)-1-methyl-5-indolamine and bromoacetic acid-N,N-bis-(methoxycarbonylmethyl)-amide.
Yield: 43% of theory

c) 3-[3-(4-amidinophenyl)-propionyl]-N-[bis-(methoxycarbonylmethyl)-aminocarbonylmethyl]-N-(8-quinolinylsulfonyl)-1-methyl-5-indolamine hydroacetate

Produced as in example 79 from 3-]3-(4-cyanophenyl)-propionyl]-N-[bis-(methoxycarbonylmethyl)-aminocarbonylmethyl]-N-(8-quinolinylsulfonyl)-1-methyl-5-indolamine with hydrogen sulfide, methyliodide and ammonium acetate.
Yield: 60% of theory
Melting point: 212°C (decomp.)
$C_{36}H_{36}N_6O_8S$ (712.79)
Mass spectrum: $(M+H)^+ = 713$

Example 114

3-[3-(4-amidinophenyl)-propionyl]-N-[bis-(hydroxycarbonylmethyl)-aminocarbonylmethyl]-N-(8-quinolinylsulfonyl)-1-methyl-5-indolamine hydrochloride

---

Produced as in example 2 by saponification of N-[bis-(methoxycarbonylmethyl)-aminocarbonylmethyl]-N-(8-quinolinylsulfonyl)-3-[3-(4-amidinophenyl)-propionyl]-1-methyl-5-indolamine hydroacetate.
Yield: 83% of theory
Melting point: 200°C (decomp.)
$C_{34}H_{32}N_6O_8S$ (684.73)
Mass spectrum: $(M+H)^+ = 685$

Example 115

3-[3-(4-amidinophenyl)-propionyl]-N-(2-methoxycarbonylethylaminocarbonyl-methyl)-N-(8-quinolinylsulfonyl)-1-methyl-5-indolamine hydroiodide

---

Produced as in example 113 by reaction of 3-]3-(4-cyanophenyl)-propionyl]-N-(2-methoxycarbonylethylaminocarbonylmethyl)-N-(8-quinolinylsulfonyl)-1-methyl-5-indolamine with hydrogen sulfide, methyliodide and ammonium acetate.
Yield: 83% of theory
Melting point: 130°C (decomp.)
$C_{34}H_{34}N_6O_6S$ (654.75)
Mass spectrum: $(M+H)^+ = 655$

Example 116

3-[3-(4-amidinophenyl)-propionyl]-N-(2-hydroxycarbonylethylaminocarbonyl-methyl]-N-(8-quinolinylsulfonyl)-1-methyl-5-indolamine hydrochloride

---

Produced as in example 2 by saponification of 3-{3-(4-amidinophenyl)-propionyl]-N-(2-methoxycarbonylethylaminocarbonylmethyl)-N-(8-quinolinylsulfonyl)-1-methyl-5-indolamine hydroiodide.
Yield: 85% of theory
Melting point: 200°C (decomp.)
$C_{33}H_{32}N_6O_6S$ (640.72)

Example 117

3-[3-(4-amidinophenyl)-propionyl]-N-[(N-methoxycarbonylmethyl-N-methylamino)-carbonylmethyl]-N-(8-quinolinylsulfonyl)-1-methyl-5-indolamine hydroiodide

---

Produced as in example 113 from 3-[3-(4-cyanophenyl)-propionyl]-N-[(N-methoxycarbonylmethyl-N-methylamino)carbonylmethyl]-N-(8-quinolinylsulfonyl)-1-methyl-5-indolamine with hydrogen sulfide, methyliodide and ammonium acetate.
Yield: 51% of theory
$C_{34}H_{34}N_6O_6S$ (654.75)
R_f value: 0.23 (silica gel; dichloromethane/ethanol = 9:1)
Mass spectrum: $(M+H)^+ = 655$

Example 118

3-[3-(4-amidinophenyl)-propionyl]-N-[(N-hydroxycarbonylmethyl-N-methylamino)-carbonylmethyl]-N-(8-quinolinylsulfonyl)-1-methyl-5-indolamine hydrochloride

---

Produced as in example 2 by saponification of 3-{3-(4-amidinophenyl)-propionyl]-N-[(N-methoxycarbonylmethyl-N-methylamino)-carbonylmethyl]-N-(8-quinolinylsulfonyl)-1-methyl-5-indolamine hydroiodide.
Yield: 73% of theory
Melting point: 230°C (decomp.)
$C_{33}H_{32}N_6O_6S$ (640.72)
Mass spectrum: $(M+H)^+ = 641$

Example 119

3-[3-(4-amidinophenyl)-propionyl]-N-(2-ethoxycarbonylethyl)-N-(8-quinolinylsulfonyl)-1-methyl-5-indolamine hydrochloride

---

Produced as in example 65 by reaction of 3-[3-(4-cyanophenyl)-propionyl]-N-(2-ethoxycarbonylethyl)-N-(8-quinolinylsulfonyl)-1-methyl-5-indolamine with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 73% of theory
Melting point: 175°C (decomp.)
$C_{33}H_{33}N_5O_5S$ (611.73)
Mass spectrum: $(M+H)^+ = 612$

Example 120

3-[3-(4-amidinophenyl)-propionyl]-N-(2-hydroxycarbonylethyl-N-(8-quinolinylsulfonyl)-1-methyl-5-indolamine hydrochloride

---

Produced as in example 2 by saponification of 3-{3-(4-amidinophenyl)-propionyl]-N-(2-ethoxycarbonylethyl)-N-(8-quinolinylsulfonyl)-1-methyl-5-indolamine.
Yield: 87% of theory
Melting point: 284°C
$C_{31}H_{29}N_5O_5S$ (583.67)
Mass spectrum: $(M+H)^+ = 584$

Example 121

3-[3-(4-amidinophenyl)-propionyl]-N-(3-ethoxycarbonylpropyl)-N-(8-quinolinylsulfonyl)-1-methyl-5-indolamine hydrochloride

---

Produced as in example 76 by reaction of 3-[3-(4-cyanophenyl)-propionyl]-N-(3-ethoxycarbonylpropyl)-N-(8-quinolinylsulfonyl)-1-methyl-5-indolamine with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 62% of theory
R_f value: 0.15 (silica gel; dichloromethane/ethanol = 9:1)
$C_{34}H_{35}N_5O_5S$ (625.75)
Mass spectrum: $(M+H)^+ = 626$

Example 122

3-[3-(4-cyanophenyl)-propionyl]-N-(3-hydroxycarbonylpropyl)-N-8-quinolinylsulfonyl)-1-methyl-5-indolamine hydrochloride

---

Produced as in example 2 by saponification of 3-{3-(4-cyanophenyl)-propionyl]-N-(3-ethoxycarbonylpropyl)-N-(8-quinolinylsulfonyl)-1-methyl-5-indolamine hydrochloride.
Yield: 99% of theory
Melting point: 95°C (decomp.)
$C_{32}H_{31}N_5O_5S$ (597.70)
Mass spectrum: $(M+H)^+ = 598$

Example 123

5-(8-quinoline sulfonamido)-1-methylindole-3-carboxylic acid-4-amidinophenyl-amide hydrochloride

---

a) 1-methyl-5-nitroindole-3-carboxylic acid methylester

16.8 g (150 mmol) potassium tert.butylate are added in portions at room temperature to a solution of 10.8 g (52.3 mmol) 5-nitroindole-3-carboxylic acid in 150 ml DMF. After 20 minutes of stirring at 0°C, 10 ml (22.7 g, 160 mmol) methyliodide are dissolved at room temperature. Yield: 30 ml DMF added in drops [sic]. The mixture is then allowed to warm up to room temperature and is then heated for 3 hours to 80°C. The solvent is then removed *in vacuo* and the residue is divided between dichloromethane and water. The organic phase is dried over sodium sulfate and the residue obtained after the solvent is removed is chromatographed on silica gel (dichloromethane).
Yield: 5.6 g (46% of theory)
Melting point: 162°C

b) 1-methyl-5-nitroindole-3-carboxylic acid

Produced as in example 2 by saponification of 1-methyl-5-nitroindole-3-carboxylic acid methylester.
Yield: 91% of theory
Melting point: 275°C (decomp.)

c) 1-methyl-5-nitroindole-3-carboxylic acid chloride

A solution of 2.2 g (10 mmol) 1-methyl-5-nitroindole-3-carboxylic acid and 70 ml thionyl chloride in 20 ml dichloromethane is heated to boiling for 4 hours. The solution is then drawn off from the insoluble part and the filtrate is freed of the solvent *in vacuo*. The residue obtained is triturated with ether.
Yield: 1.9 g (80% of theory)
$C_{10}H_7ClN_2O_3$ (238.67)
Melting point: 186°C
Mass spectrum: $(M+H)^+ = 240, 238$

d) 1-methyl-5-nitroindole-3-carboxylic acid-(4-cyanophenyl)-amide

Produced as in example 1f from 1-methyl-5-nitroindole-3-carboxylic acid chloride and 4-aminobenzonitrile.
Yield: 79% of theory
Melting point: >278°C

e) 5-amino-1-methylindole-3-carboxylic acid-(4-cyanophenyl)-amide

Produced as in example 49c by catalytic hydration of 1-methyl-5-nitroindole-3-carboxylic acid-(4-cyanophenyl)-amide in DMF.
Yield: 68% of theory
Melting point: 144°C (decomp.)

f) 5-(8-quinoline sulfonamido)-1-methylindole-3-carboxylic acid-(4-cyanophenyl)-amide

Produced as in example 75a from 5-amino-1-methylindole-3-carboxylic acid-(4-cyanophenyl)-amide and 8-quinoline sulfonic acid chloride.
Yield: 74% of theory
Melting point: 278°C (decomp.)

g) 5-(8-quinoline sulfonamido)-1-methylindole-3-carboxylic acid-4-amidinophenyl-amide hydrochloride

Produced as in example 1g by reaction of 5-(8-quinoline sulfonamido)-1-methylindole-3-carboxylic acid-(4-cyanophenyl)-amide with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 90% of theory
Melting point: >270°C (decomp.)
$C_{26}H_{22}N_6O_3S$ (498.57)
Mass spectrum: $(M+H)^+ = 499$

Example 124

3-(4-amidinophenylmethylaminocarbonyl)-N-phenylsulfonyl-1-methyl-5-indolamine hydrochloride

---

a) 1-methyl-5-nitroindole-3-carboxylic acid-(4-cyanophenylmethyl)-amide

14.0 g (63 mmol) 1-methyl-5-nitroindole-3-carboxylic acid (example 123b) are suspended in 150 ml DMF and mixed with 30 ml (22g, 215 mmol) triethylamine. 20.9 g (65 mmol) TBTU, 8.8 g (65 mmol) HOBt and 13.5 g (80 mmol) 4-cyanobenzylamine hydrochloride are added in succession under nitrogen at room temperature with stirring. After 2 hours of stirring, the precipitated product is drawn off and washed with water and acetone.
Yield: 15.5 g (74% of theory)
$C_{18}H_{14}N_4O_3$ (334.3)
Melting point: 264°C (DMF/ethanol)

Calculated: C 64.67 H 4.22 N 16.76
Found: C 64.48 H 4.45 N 16.72

b) 5-amino-1-methylindole-3-carboxylic acid-(4-cyanophenylmethyl)-amide

Produced as in example 123e by catalytic hydration of 1-methyl-5-nitroindole-3-carboxylic acid-(4-cyanophenylmethyl)-amide.
Yield: 82% of theory
Melting point: 208°C

c) 3-(4-cyanophenylmethylaminocarbonyl)-N-phenylsulfonyl-1-methyl-5-indolamine

Produced as in example 123f from 5-amino-1-methylindole-3-carboxylic acid-(4-cyanophenylmethyl)-amide and benzene sulfonic acid chloride.
Yield: 90% of theory
$C_{24}H_{20}N_4O_3$ (444.52)
Melting point: 178°C
Mass spectrum: $M^+ = 444$
Calculated: C 64.85 H 4.55 N 12.60
Found: C 64.72 H 4.66 N 12.67

d) 3-(4-amidinophenylmethylaminocarbonyl)-N-phenylsulfonyl-1-methyl-5-indolamine hydrochloride

Produced as in example 123g by reaction of 3-(4-cyanophenylmethylaminocarbonyl)-N-phenylsulfonyl-1-methyl-5-indolamine with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 93% of theory
$C_{24}H_{23}N_5O_3S$ (461.55)
Melting point: starting at 145°C (decomp.)
Mass spectrum: $(M+H)^+ = 462$

Example 125

3-(4-amidinophenylmethylaminocarbonyl)-N-(2,5-dichlorobenzene sulfonamido)-1-methyl-5-indolamine hydrochloride

---

Produced as in example 123 by reaction of 3-(4-cyanophenylmethylaminocarbonyl)-N-(2,5-dichlorobenzene sulfonamido)-1-methyl-5-indolamine hydrochloride with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 90% of theory
Melting point: 190°C
$C_{24}H_{21}Cl_2N_5O_3S$ (530.44)
Mass spectrum: $(M+H)^+ = 534, 532, 530$

Example 126

3-(4-amidinophenylmethylaminocarbonyl)-N-(5-isoquinoline sulfonamido)-1-methyl-5-indolamine hydrochloride

---

Produced as in example 123 by reaction of 3-(4-cyanophenylmethylaminocarbonyl)-N-(5-isoquinoline sulfonamido)-1-methyl-5-indolamine with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 73% of theory
Melting point: starting at 290°C
$C_{27}H_{24}N_6O_3S$ (512.60)
Mass spectrum: $(M+H)^+ = 513$

Example 127

3-(4-amidinophenylmethylaminocarbonyl)-N-(5-isoquinolinylsulfonyl)-N-ethoxycarbonylmethyl-1-methyl-5-indolamine hydrochloride

---

Produced as in examples 76 and 123 by reaction of 3-(4-cyanophenylmethylaminocarbonyl)-N-(5-isoquinolinylsulfonyl)-N-ethoxycarbonylmethyl-1-methyl-5-indolamine with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 86% of theory
Melting point: starting at 150°C
$C_{31}H_{30}N_6O_5S$ (598.69)
Mass spectrum: $(M+H)^+ = 599$

Example 128

3-(4-amidinophenylmethylaminocarbonyl)-N-(5-isoquinolinylsulfonyl)-N-hydroxycarbonylmethyl-1-methyl-5-indolamine

---

A solution of 1.0 g (1.5 mmol) 3-(4-amidinophenylmethylaminocarbonyl)-N-(5-isoquinolinylsulfonyl)-N-ethoxycarbonylmethyl-1-methyl-5-indolamine hydrochloride in 15 ml methanol is mixed with 7.5 ml 1N caustic soda solution. The mixture is stirred for 2 hours at room temperature and then diluted with water. The reaction solution is neutralized with 1N hydrochloric acid to pH 7, mixed with ethyl acetate and stirred. The precipitated product is drawn off and washed with water, ethanol and ether.
Yield: 0.85 g (96% of theory)
Melting point: starting at 250°C (decomp.)
$C_{29}H_{26}N_6O_5S$ (570.63)
Mass spectrum: $(M+H)^+ = 571$
$C_{29}H_{26}N_6O_5S \times H_2O$ (588.65)
Calculated: C 59.17 H 4.79 N 14.28
Found: C 59.26 H 4.90 N 14.33

Example 129

3-(4-amidinophenylmethylaminocarbonyl)-N-(8-quinolinylsulfonyl)-1-methyl-5-indolamine hydrochloride

---

Produced as in example 123 by reaction of 3-(4-cyanophenylmethylaminocarbonyl)-N-(8-quinolinylsulfonyl)-1-methyl-5-indolamine with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 90% of theory
Melting point: 200°C (decomp.)
$C_{27}H_{24}N_6O_3S$ (512.60)
Mass spectrum: $(M+H)^+ = 513$

Example 130

3-(4-amidinophenylmethylaminocarbonyl)-N-(8-quinolinylsulfonyl)-N-ethoxycarbonylmethyl-1-methyl-5-indolamine hydrochloride

---

Produced as in example 127 by reaction of 3-(4-cyanophenylmethylaminocarbonyl)-N-(8-quinolinylsulfonyl)-N-ethoxycarbonylmethyl-1-methyl-5-indolamine with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 86% of theory
Melting point: starting at 190°C
$C_{31}H_{30}N_6O_5S$ (598.69)
Mass spectrum: $(M+H)^+ = 599$

Example 131

3-(4-amidinophenylmethylaminocarbonyl)-N-(8-quinolinylsulfonyl)-N-hydroxycarbonylmethyl-1-methyl-5-indolamine

---

Produced as in example 128 by saponification of 3-(4-amidinophenylmethylaminocarbonyl)-N-(8-quinolinylsulfonyl)-N-ethoxycarbonylmethyl-1-methyl-5-indolamine hydrochloride.
Yield: 96% of theory
Melting point: starting at 255°C
$C_{29}H_{26}N_6O_5S$ (570.63)
Mass spectrum: $(M+H)^+ = 571$

Example 132

3-[2-methyl-3-(4-amidinophenyl)-propionyl]-N-methoxycarbonylmethylamino-carbonylmethyl-N-(8-quinolinylsulfonyl)-1-methyl-5-indolamine hydroiodide

---

a) 2-methyl-3-(4-cyanophenyl)-propionic acid

2.3 g (48 mmol) sodium hydride are added in portions at room temperature to a solution of 9.5 g (40 mmol) 2-phosphonopropionic acid triethylester in 50 ml dioxane. The mixture is stirred for 30 minutes and a solution of 5.24 g (40 mmol) 4-cyanobenzaldehyde is then added in drops at 15-18°C. After 60 minutes of stirring at room temperature, ice water is added and extraction is performed with ethyl acetate. The organic phase is dried over sodium sulfate and, after removal of the solvent *in vacuo*, the residue obtained is chromatographed on silica gel (cyclohexane/toluene/ethyl acetate = 16:4:1). The product thus obtained is dissolved in 60 ml ethanol, mixed with 1.5 g palladium/carbon (5%) and hydrated for 10 minutes in a hydrogen atmosphere at 3.4 bar. The residue obtained after removal of the catalyst and concentration by evaporation is absorbed in dichloromethane and washed with dilute hydrochloric acid. The organic phase is dried over sodium sulfate and freed of the solvent *in vacuo*. The product thus obtained is dissolved in 50 ml methanol and mixed with 6 g sodium hydroxide dissolved in 100 ml water. The mixture is stirred for 60 minutes at room temperature, then acidified with dilute hydrochloric acid and extracted with dichloromethane. The organic phase is dried over sodium sulfate, concentrated to dryness and the residue is triturated with petroleum ether.
Yield: 3.6 g (49% of theory)
$C_{11}H_{11}NO_2$ (189.2)
Melting point: 95°C
Calculated: C 69.83 H 5.85 N 7.39
Found: C 69.59 H 5.96 N 7.20

b) 2-methyl-3-(4-cyanophenyl)-propionic acid chloride

1.9 g (10 mmol) 2-methyl-3-(4-cyanophenyl)-propionic acid are heated overnight to reflux in 15 ml thionyl chloride. The thionyl chloride is then removed *in vacuo* and the residue is triturated with petroleum ether. The oil obtained after the solvent is evaporated off is dried *in vacuo*.

Yield: 2.1 g (99% of theory; yellow oil)
$C_{11}H_{10}ClNO$ (207.7)
Calculated: C 63.61 H 4.85 N 6.74
Found: C 63.33 H 4.96 N 6.51

c) 3-[2-methyl-3-(4-cyanophenyl)-propionyl]-1-methyl-5-indolamine

Produced as in example 49 by Friedel-Crafts acylation of 1-methyl-5-nitroindole with 2-methyl-3-(4-cyanophenyl)-propionic acid chloride followed by catalytic hydration.
Yield: 57% of theory
Melting point: 175°C (decomp.)

d) 3-[2-methyl-3-(4-cyanophenyl)-propionyl]-N-(8-quinolinylsulfonyl)-1-methyl-5-indolamine

Produced as in example 75a from 3-[2-methyl-3-(4-amidinophenyl)-propionyl]-1-methyl-5-indolamine and 8-quinoline-sulfonic acid chloride in pyridine.
Yield: 69% of theory
Melting point: 230°C (decomp.)
$C_{29}H_{24}N_4O_3S$ (508.6)
Calculated: C 68.48 H 4.75 N 11.01
Found: C 68.70 H 4.95 N 11.05

e) 3-[2-methyl-3-(4-cyanophenyl)-propionyl]-N-methoxycarbonylmethylamino-carbonylmethyl-N-(8-quinolinylsulfonyl)-1-methyl-5-indolamine

Produced as in example 76a from N-(8-quinolinylsulfonyl)-3-[2-methyl-3-(4-amidinophenyl)-propionyl]-1-methyl-5-indolamine and bromoacetic acid-N-methoxycarbonylmethyl-amide.
Yield: 97% of theory (foamy product).

f) 3-[2-methyl-3-(4-amidinophenyl)-propionyl]-N-methoxycarbonylmethylamino-carbonylmethyl-N-(8-quinolinylsulfonyl)-1-methyl-5-indolamine hydroiodide

Produced as in example 79 from 3.-[2-methyl-3-(4-cyanophenyl)-propionyl]-N-methoxycarbonylmethylaminocarbonylmethyl-N-(8-quinolinylsulfonyl)-1-methyl-5-indolamine with hydrogen sulfide, methyliodide and ammonium acetate.
Yield: 74% of theory
Melting point: starting at 90°C (decomp.)
$C_{34}H_{34}N_6O_6S$ (654.75)
Mass spectrum: $(M+H)^+ = 655$

Example 133

3-[2-methyl-3-(4-amidinophenyl)-propionyl]-N-hydroxycarbonylmethylamino-carbonylmethyl-N-(8-quinolinylsulfonyl)-1-methyl-5-indolamine hydroiodide

---

Produced as in example 2 by saponification of 3-[2-methyl-3-(4-amidinophenyl)-propionyl]-N-methoxycarbonylmethylaminocarbonylmethyl-N-(8-quinolinylsulfonyl)-1-methyl-5-indolamine hydroiodide.
Yield: 81% of theory
Melting point: starting at 220°C (decomp.)
$C_{33}H_{32}N_6O_6S$ (640.72)
Mass spectrum: $(M+H)^+ = 641$

Example 134

3-(4-amidinophenoxyacetyl)-N-(8-quinolinylsulfonyl)-1-methyl-5-indolamine hydroiodide

---

a) 3-(4-cyanophenoxyacetyl)-1-methyl-5-nitroindole

Produced as in example 49b by Friedel-Crafts acylation of 1-methyl-5-nitroindole with (4-cyanophenoxy)-acetic acid chloride.
Yield: 19% of theory
Melting point: 250°C

b) 3-(4-cyanophenoxyacetyl)-1-methyl-5-indolamine

Produced as in example 49c by catalytic hydration of 3-(4-cyanophenoxyacetyl)-1-methyl-5-nitroindole.
Yield: 82% of theory
Melting point: 183°C (decomp.)

c) 3-(4-cyanophenoxyacetyl)-N-(8-quinolinylsulfonyl)-1-methyl-5-indolamine

Produced as in example 75a from 3-(4-cyanophenoxyacetyl)-1-methyl-5-indolamine and 8-quinoline-sulfonic acid chloride.
Yield: 68% of theory

d) 3-(4-amidinophenoxyacetyl)-N-(8-quinolinylsulfonyl)-1-methyl-5-indolamine hydroiodide

Produced as in example 79 from 3-(4-cyanophenoxyacetyl)-N-(8-quinolinylsulfonyl)-1-methyl-5-indolamine with H_2S, methyliodide and ammonium acetate.
Yield: 31% of theory
Melting point: 90°C (decomp.)
$C_{27}H_{23}N_5O_4S$ (513.58)
Mass spectrum: $(M+H)^+ = 514$

Example 135

3-(4-amidinophenoxyacetyl)-N-ethoxycarbonylmethyl-N-(8-quinolinylsulfonyl)-1-methyl-5-indolamine-hydroiodide

---

a) 3-(4-cyanophenoxyacetyl)-N-ethoxycarbonylmethyl-N-(8-quinolinylsulfonyl)-1-methyl-5-indolamine

Produced as in example 76a from 3-(4-cyanophenoxyacetyl)-N-(8-quinolinylsulfonyl)-1-methyl-5-indolamine and bromoacetic acid ethylester.
Yield: 86% of theory
Melting point: 198°C

b) 3-(4-amidinophenoxyacetyl)-N-ethoxycarbonylmethyl-N-(8-quinolinylsulfonyl)-1-methyl-5-indolamine hydroiodide

Produced as in example 21 from 3-(4-cyanophenoxyacetyl)-N-ethoxycarbonylmethyl-N-(8-quinolinylsulfonyl)-1-methyl-5-indolamine with hydrogen sulfide, methyliodide and ammonium acetate.
Yield: 16% of theory
Melting point: 100°C (decomp.)
$C_{31}H_{29}N_5O_6S$ (599.67)
Mass spectrum: $(M+H)^+ = 600$

Example 136

3-(4-amidinophenylacetyl)-N-ethoxycarbonylmethyl-N-valeryl-1-methyl-5-indolamine hydrochloride

---

a) 3-(4-cyanophenylacetyl)-1-methyl-5-nitroindole

Produced as in example 49b by Friedel-Crafts acylation of 1-methyl-5-nitroindole with 4-cyanophenylacetic acid chloride.
Yield: 25% of theory
Melting point: 256-258°C

b) 3-(4-cyanophenylacetyl)-1-methyl-5-indolamine

Produced as in example 49c by catalytic hydration of 3-(4-cyanophenylacetyl)-1-methyl-5-nitroindole.
Yield: 86% of theory
Melting point: 130°C (decomp.)

c) 3-(4-cyanophenylacetyl)-N-ethoxycarbonylmethyl-1-methyl-5-indolamine

Produced as in example 49d from 3-(4-cyanophenylacetyl)-1-methyl-5-indolamine and iodoacetic acid ethylester.
Yield: 35% of theory
Melting point: 142°C (decomp.)

d) 3-(4-cyanophenylacetyl)-N-ethoxycarbonylmethyl-N-valeryl-1-methyl-5-indolamine

Produced as in example 49e from 3-(4-cyanophenylacetyl)-N-ethoxycarbonylmethyl-1-methyl-5-indolamine and valeryl chloride.
Yield: 82% yield as thick oil.

e) 3-(4-amidinophenylacetyl)-N-ethoxycarbonylmethyl-N-valeryl-1-methyl-5-indolamine hydrochloride

Produced as in example 1g by reaction of 3-(4-cyanophenylacetyl)-N-ethoxycarbonylmethyl-N-valeryl-1-methyl-5-indolamine with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 81% of theory
Melting point: 144°C (decomp.)
$C_{27}H_{32}N_4O_4$ (476.58)
Mass spectrum: $(M+H)^+ = 477$

Example 137

3-(4-amidinophenylacetyl)-N-hydroxycarbonylmethyl-N-valeryl-1-methyl-5-indolamine hydrochloride

---

Produced as in example 2 by saponification of 3-(4-amidinophenylacetyl)-N-ethoxycarbonylmethyl-N-valeryl-1-methyl-5-indolamine hydrochloride.
Yield: 89% of theory
Melting point: starting at 95°C (decomp.)
$C_{25}H_{28}N_4O_4$ (448.53)
Mass spectrum: $(M+H)^+ = 449$

Example 138

3-(4-amidinophenylacetyl)-N-ethoxycarbonylmethyl-N-(2-pyridylcarbonyl)-1-methyl-5-indolamine hydrochloride

---

Produced as in example 136 by reaction of 3-(4-cyanophenylacetyl)-N-ethoxycarbonylmethyl-N-(2-pyridylcarbonyl)-1-methyl-5-indolamine with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 84% of theory
Melting point: starting at 140°C (decomp.)
$C_{28}H_{27}N_5O_4$ (497.56)
Mass spectrum: $(M+H)^+ = 498$

Example 139

3-(4-amidinophenylacetyl)-N-hydroxycarbonylmethyl-N-(2-pyridylcarbonyl)-1-methyl-5-indolamine hydrochloride

---

Produced as in example 2 by saponification of 3-(4-amidinophenylacetyl)-N-ethoxycarbonylmethyl-N-(2-pyridylcarbonyl)-1-methyl-5-indolamine hydrochloride.
Yield: 92% of theory

Melting point: 115°C (decomp.)
$C_{26}H_{23}N_5O_4$ (469.50)
Mass spectrum: $(M+H)^+ = 470$

Example 140

3-(4-amidinophenylacetyl)-N-ethoxycarbonylmethyl-N-(3-pyridylcarbonyl)-1-methyl-5-indolamine hydrochloride

---

Produced as in example 136 by reaction of 3-(4-cyanophenylacetyl)-N-ethoxycarbonylmethyl-N-(3-pyridylcarbonyl)-1-methyl-5-indolamine hydrochloride with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 98% of theory
Melting point: starting at 140°C (decomp.)
$C_{28}H_{27}N_5O_4$ (497.56)
Mass spectrum: $(M+H)^+ = 498$

Example 141

3-(4-amidinophenylacetyl)-N-hydroxycarbonylmethyl-N-(3-pyridylcarbonyl)-1-methyl-5-indolamine hydrochloride

---

Produced as in example 2 by saponification of 3-(4-amidinophenylacetyl)-N-ethoxycarbonylmethyl-N-(3-pyridylcarbonyl)-1-methyl-5-indolamine hydrochloride.
Yield: 92% of theory
Melting point: 205°C (decomp.)
$C_{26}H_{23}N_5O_4$ (469.50)
Mass spectrum: $(M+H)^+ = 470$

Example 142

3-(4-amidinophenylacetyl)-N-ethoxycarbonylmethyl-N-(4-pyridylcarbonyl)-1-methyl-5-indolamine hydrochloride

---

Produced as in example 136 by reaction of 3-(4-cyanophenylacetyl)-N-ethoxycarbonylmethyl-N-(4-pyridylcarbonyl)-1-methyl-5-indolamine with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 76% of theory
Melting point: starting at 148°C (decomp.)
$C_{28}H_{27}N_5O_4$ (497.56)
Mass spectrum: $(M+H)^+ = 498$

Example 143

3-(4-amidinophenylacetyl)-N-hydroxycarbonylmethyl-N-(4-pyridylcarbonyl)-1-methyl-5-indolamine dihydrochloride

---

Produced as in example 2 by saponification of N-ethoxycarbonylmethyl-N-(4-pyridylcarbonyl)-3-(4-amidinophenylacetyl)-1-methyl-5-indolamine hydrochloride.
Yield: 84% of theory
Melting point: 105°C (decomp.)
$C_{26}H_{23}N_5O_4$ (469.50)
Mass spectrum: $(M+H)^+ = 470$

Example 144

3-(4-amidinophenylacetyl)-N-(8-quinolinylsulfonyl)-1-methyl-5-indolamine hydrochloride

---

Produced as in example 75 by reaction of 3-(4-cyanophenylacetyl)-N-8-quinolinylsulfonyl)-1-methyl-5-indolamine with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 77% of theory
Melting point: 227°C (decomp.)
$C_{27}H_{23}N_5O_3S$ (497.58)
Mass spectrum: $(M+H)^+ = 498$

Example 145

3-(4-amidinophenylacetyl)-N-ethoxycarbonylmethyl-N-(8-quinolinylsulfonyl)-1-methyl-5-indolamine hydrochloride

---

Produced as in example 76 by reaction of 3-(4-cyanophenylacetyl)-N-ethoxycarbonylmethyl-N-(8 quinolinylsulfonyl)-1-methyl-5-indolamine with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 46% of theory
Melting point: 190°C (decomp.)
$C_{31}H_{29}N_5O_5S$ (583.67)
Mass spectrum: $(M+H)^+ = 584$

Example 146

3-(4-amidinophenylacetyl)-N-hydroxycarbonylmethyl-N-(8-quinolinylsulfonyl)-1-methyl-5-indolamine hydrochloride

---

Produced as in example 2 by saponification of 3-(4-amidinophenylacetyl)-N-ethoxycarbonylmethyl-N-(8-quinolinylsulfonyl)-1-methyl-5-indolamine hydrochloride.
Yield: 84% of theory
Melting point: 238°C
$C_{29}H_{25}N_5O_5S$ (555.62)

Example 147

3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-6-carboxylic acid-N-ethoxycarbonylmethyl-N-phenyl-amide-hydrochloride

---

a) 4-(2-dimethoxyethyl)-3-nitrobenzoic acid

A solution of 3.5 g (62 mmol) potassium hydroxide and 3.4 g (12 mmol) 4-(trimethylsilylethinyl)-3-nitrobenzoic acid in 62 ml methanol is heated to reflux for 20 minutes. The reaction solution is then cooled to room temperature and mixed with 3.4 g (62 mmol) glacial acetic acid and 400 ml water. After extraction with dichloromethane, the organic phase is concentrated to dryness and the residue is triturated with petroleum ether.
Yield: 2.3 g (73% of theory)
Melting point: 116-118°C
$C_{30}H_{30}N_4H_4$ (510.60)

b) Indole-6-carboxylic acid

2.3 g 4-(2-dimethoxyethyl)-3-nitrobenzoic acid are dissolved in 100 ml methanol and hydrated over palladium/carbon (5%) for 40 minutes at room temperature and at a hydrogen pressure of 3.4 bar. The catalyst is filtered off and the reaction solution is concentrated to dryness. The residue is dissolved in 10 ml ethanol and mixed with 10 ml 1N hydrochloric acid. The reaction solution is heated for 40 minutes to 70°C, then cooled to room temperature and mixed with 30 ml water. The product precipitates out, is drawn off and dried.
Yield: 640 mg (44% of theory)
Melting point: 254°C

c) 1-methylindole-6-carboxylic acid methylester

Produced as in example 1a from indole-6-carboxylic acid, potassium tert.butylate and methyliodide in DMSO.
Yield: 64% of theory (brown oil)

d) 3-[3-(4-cyanophenyl)-propionyl]-1-methylindole-6-carboxylic acid-methylester

Produced as in example 1c by Friedel-Crafts acylation of 1-methylindole-6-carboxylic acid methylester with 3-(4-cyanophenyl)-propionic acid chloride.
Yield: 74% of theory

e) 3-[3-(4-cyanophenyl)-propionyl]-1-methylindole-6-carboxylic acid

Produced as in example 2 by saponification of 3-[3-(4-cyanophenyl)-propionyl]-1-methylindole-6-carboxylic acid methylester.
Yield: 85% of theory

f) 3-[3-(4-cyanophenyl)-propionyl]-1-methylindole-6-carboxylic acid-N-ethoxycarbonylmethyl-N-phenyl-amide

Produced as in example 1f from 3-[3-(4-cyanophenyl)-propionyl]-1-methylindole-6-carboxylic acid, thionyl chloride and N-phenylglycine ethylester
Yield: 56% of theory

g) 3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-6-carboxylic acid-N-ethoxycarbonylmethyl-N-phenyl-amide hydrochloride

Produced as in example 1g by reaction of 3-[3-(4-cyanophenyl)-propionyl]-1-methylindole-6-carboxylic acid-N-ethoxycarbonylmethyl-N-phenyl-amide with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 46% of theory
Melting point: 86°C (decomp.)

Example 148

3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-6-carboxylic acid-N-hydroxycarbonylmethyl-N-phenyl-amide hydrochloride

---

Produced as in example 2 by saponification of 3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-6-carboxylic acid-N-ethoxycarbonylmethyl-N-phenyl-amide hydrochloride.
Yield: 77% of theory
Melting point: 218°C
$C_{28}H_{26}N_4O_4$ (482.54)
Mass spectrum: $(M+H)^+ = 484$

Example 149

3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-6-carboxylic acid-N-ethoxycarbonylmethyl-N-(2-pyridyl)-amide hydrochloride

---

Produced as in example 147 by reaction of 3-[3-(4-cyanophenyl)-propionyl]-1-methylindole-6-carboxylic acid-N-ethoxycarbonylmethyl-N-(2-pyridyl)-amide with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 24% of theory (foamy product)
$C_{29}H_{29}N_5O_4$ (511.59)
Mass spectrum: $(M+H)^+ = 512$

Example 150

3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-6-carboxylic acid-N-hydroxycarbonylmethyl-N-(2-pyridyl)-amide hydrochloride

---

Produced as in example 2 by saponification of 3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-6-carboxylic acid-N-ethoxycarbonylmethyl-N-(2-pyridyl)-amide hydrochloride.
Yield: 75% of theory (foamy product)
$C_{27}H_{25}N_5O_4$ (483.53)
Mass spectrum: $(M+H)^+ = 484$

Example 151

3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-6-carboxylic acid-N-ethoxycarbonylmethylaminocarbonylmethyl-N-(2-pyridyl)-amide hydrochloride

---

Produced as in example 147 by reaction of 3-[3-(4-cyanophenyl)-propionyl]-1-methylindole-6-carboxylic acid-N-ethoxycarbonylmethylaminocarbonylmethyl-N-(2-pyridyl)-amide with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 14% of theory
Melting point: starting at 76°C (decomp.)
$C_{31}H_{32}N_6O_5$ (568.64)

Example 152

3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-6-carboxylic acid-N-ethoxycarbonylethyl-N-(2-pyridyl)-amide hydrochloride

---

Produced as in example 147 by reaction of 3-[3-(4-cyanophenyl)-propionyl]-1-methylindole-6-carboxylic acid-N-ethoxycarbonylethyl-N-(2-pyridyl)-amide with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 42% of theory
Melting point: 85°C (decomp.)
$C_{30}H_{31}N_5O_4$ (525.61)

Example 153

3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-6-carboxylic acid-N-hydroxycarbonylethyl-N-(2-pyridyl)-amide hydrochloride

---

Produced as in example 2 by saponification of 3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-6-carboxylic acid-N-ethoxycarbonylethyl-N-(2-pyridyl)-amide hydrochloride.
Yield: 79% of theory

$C_{28}H_{27}N_5O_4$ (497.56)
Mass spectrum: $(M+H)^+ = 498$

Example 154

3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-6-carboxylic acid-N-ethoxycarbonylmethyl-N-(8-quinolinyl)-amide hydrochloride

---

Produced as in example 147 by reaction of 3-[3-(4-cyanophenyl)-propionyl]-1-methylindole-6-carboxylic acid-N-ethoxycarbonylmethyl-N-(8-quinolinyl)-amide with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 70% of theory
Malting point: 108°C (decomp.)
$C_{33}H_{31}N_5O_4$ (561.65)

Example 155

3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-6-carboxylic acid-N-hydroxycarbonylmethyl-N-(8-quinolinyl)-amide hydrochloride

---

Produced as in example 2 by saponification of 3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-6-carboxylic acid-N-ethoxycarbonylmethyl-N-(8-quinolinyl)-amide hydrochloride.
Yield: 62% of theory
$C_{31}H_{27}N_5O_4$ (533.59)
Mass spectrum: $(M+H)^+ = 534$

Example 156

3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-6-sulfonic acid-N-methyl-N-phenyl-amide hydrochloride

---

a) 4-methyl-3-nitrobenzene-sulfonic acid chloride

35 ml concentrated nitric acid are added to 54.3 ml concentrated sulfuric acid with ice cooling. 50 g (0.26 mol) 4-toluene-sulfonic acid chloride are then added in portions with stirring, so that the reaction temperature does not exceed 40°C. The mixture is stirred for 6 hours at 40°C and stirred overnight at room temperature. It is then poured onto 500 g of ice and extracted with dichloromethane; the solvent is removed *in vacuo*.
Yield: 41 g (67% of theory; yellow oil).

b) 4-methyl-3-nitrobenzene-sulfonic acid-N-methyl-N-phenyl-amide

3.2 g (13 mmol) 4-methyl-3-nitrobenzene-sulfonic acid chloride are added in drops to a solution of 1.4 g (13 mmol) N-methylaniline in 6 ml pyridine at room temperature. After 35 minutes, the solvent is removed *in vacuo*; the residue is absorbed in dichloromethane and washed with 1N hydrochloric acid. After removal of the solvent *in vacuo* and trituration of the residue with ether, the desired product is obtained.
Yield: 3 g (75% of theory)

c) Indole-6-sulfonic acid-N-methyl-N-phenyl-amide

A solution of 2.7 g (8.8 mmol) 4-methyl-3-nitro-benzene-sulfonic acid-N-methyl-N-phenyl-amide and 3.4 ml (26 mmol) N,N,-dimethylformamide-dimethylacetal in 10 ml DMF is heated for 2 hours to 130°C. The solvent is then removed *in vacuo* and the residue is absorbed in 50 ml THF. It is then hydrated at room temperature over 0.6 g palladium/carbon (10%) for 1 hour at a hydrogen pressure of 3.4 bar. The solvent is then removed *in vacuo* and the residue is absorbed in 120 ml ethyl acetate. After washing with dilute hydrochloric acid , water and saturated sodium chloride solution, the solvent is removed.
Yield: 2.1 g (83% of theory)
R_f value: 0.44 (silica gel; toluene/ethyl acetate = 9:1)

d) 1-methylindole-6-sulfonic acid-N-methyl-N-phenyl-amide

Produced as in example 1a from indole-5-carboxylic acid, potassium tert. butylate and methyliodide in DMSO.
Yield: 65% of theory

e) 3-[3-(4-cyanophenyl)-propionyl]-1-methylindole-6-sulfonic acid-N-methyl-N-phenyl-amide

Produced as in example 1c by Friedel-Crafts acylation of 1-methylindole-6-sulfonic acid-N-methyl-N-phenyl-amide with 3-(4-cyanophenyl)-propionic acid chloride.
Yield: 68% of theory

f) 3-[3-(4-amidinophenyl)-propionyl]-1-methylindole-6-sulfonic acid-N-methyl-N-phenyl-amide hydrochloride

Produced as in example 1g by reaction of 3-[3-(4-cyanophenyl)-propionyl]-1-methylindole-6-sulfonic acid-N-methyl-N-phenyl-amide with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 20% of theory
Melting point: 194°C (decomp.)

Example 157

3-[3-(4-amidinophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-butyryl-1-methyl-6-indolamine hydrochloride

---

a) 3-[3-(4-cyanophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-butyryl-1-methyl-6-indolamine

Produced as in example 49 from 6-nitroindole by alkylation with methyliodide, Friedel-Crafts acylation with 3-(4-cyanophenyl)-propionyl chloride, catalytic hydration, alkylation with iodoacetic acid ethylester and acylation with butyric acid chloride.
Yield: 45% of theory
R_f value: 0.25 (silica gel; dichloromethane/ethyl acetate = 9:1)
$C_{27}H32N_4O_4$ (476.58)

b) 3-[3-(4-amidinophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-butyryl-1-methyl-6-indolamine hydrochloride

Produced as in example 1g by reaction of 3-[3-(4-cyanophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-butyryl-1-methyl-6-indolamine with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 75% of theory
Melting point: 77°C (decomp.)
R_f value: 0.67 (silica gel; dichloromethane/methanol = 4:1).

Example 158

3-[3-(4-amidinophenyl)-propionyl]-N-hydroxycarbonylmethyl-N-butyryl-1-methyl-6-indolamine hydrochloride

---

Produced as in example 2 by saponification of 3-[3-(4-amidinophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-butyryl-1-methyl-6-indolamine hydrochloride.
Yield: 99% of theory
R_f value: 0.06 (silica gel; dichloromethane/methanol = 4:1).
Mass spectrum: $(M+H)^+ = 449$
$C_{25}H_{28}N_4O_4$ (448.53)

Example 159

3-[3-(4-amidinophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-valeryl-1-methyl-6-indolamine hydrochloride

---

Produced as in example 157 by reaction of 3-[3-(4-cyanophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-valeryl-1-methyl-6-indolamine with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 44% of theory
Melting point: 95°C (decomp.)
R_f value: 0.55 (silica gel; dichloromethane/methanol = 4:1).
$C_{28}H_{34}N_4O_4$ (490.61)

Example 160

3-[3-(4-amidinophenyl)-propionyl]-N-hydroxycarbonylmethyl-N-valeryl-1-methyl-6-indolamine hydrochloride

---

Produced as in example 2 by saponification of 3-[3-(4-amidinophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-valeryl-1-methyl-6-indolamine hydrochloride.
Yield: 99% of theory
R_f value: 0.08 (silica gel; dichloromethane/methanol = 4:1).
Melting point: 161°C
$C_{26}H_{30}N_4O_4$ (462.55)

Example 161

3-[3-(4-amidinophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-hexanoyl-1-methyl-6-indolamine hydrochloride

---

Produced as in example 157 by reaction of 3-[3-(4-cyanophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-hexanoyl-1-methyl-6-indolamine with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 63% of theory
Melting point: 80°C
R_f value: 0.64 (silica gel; dichloromethane/methanol = 4:1).
$C_{29}H_{36}N_4O_4$ (504.64)

Example 162

3-[3-(4-amidinophenyl)-propionyl]-N-hydroxycarbonylmethyl-N-hexanoyl-1-methyl-6-indolamine hydrochloride

---

Produced as in example 2 by saponification of 3-[3-(4-amidinophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-hexanoyl-1-methyl-6-indolamine hydrochloride.
Yield: 97% of theory
$C_{27}H_{32}N_4O_4$ (476.58)
Mass spectrum: $(M+H)^+ = 477$

Example 163

3-[3-(4-amidinophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-cyclohexylcarbonyl-1-methyl-6-indolamine hydrochloride

---

Produced as in example 157 by reaction of 3-[3-(4-cyanophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-cyclohexylcarbonyl-1-methyl-6-indolamine with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 52% of theory
Melting point: 127°C
$C_{30}H_{36}N_4O_4$ (516.65)

Example 164

3-[3-(4-amidinophenyl)-propionyl]-N-hydroxycarbonylmethyl-N-cyclohexylcarbonyl-1-methyl-6-indolamine hydrochloride

---

Produced as in example 2 by saponification of 3-[3-(4-amidinophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-cyclohexylcarbonyl-1-methyl-6-indolamine hydrochloride.
Yield: 99% of theory
$C_{28}H_{32}N_4O_4$ (488.59)
Mass spectrum: $(M+H)^+ = 489$

Example 165

3-[3-(4-amidinophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-cyclohexylmethylcarbonyl-1-methyl-6-indolamine hydrochloride

---

Produced as in example 157 by reaction of 3-[3-(4-cyanophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-cyclohexylmethylcarbonyl-1-methyl-6-indolamine with ethanolic hydrochloric acid and ammonium carbonate.

Yield: 56% of theory
$C_{31}H_{38}N_4O_4$ (530.67)
Mass spectrum: $(M+H)^+ = 531$

Example 166

3-[3-(4-amidinophenyl)-propionyl]-N-hydroxycarbonylmethyl-N-cyclohexylmethylcarbonyl-1-methyl-6-indolamine hydrochloride

---

Produced as in example 2 by saponification of 3-[3-(4-amidinophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-cyclohexylmethylcarbonyl-1-methyl-6-indolamine hydrochloride.
Yield: 99% of theory
Melting point: 126°C
$C_{29}H_{34}N_4O_4$ (502.62)

Example 167

3-[3-(4-amidinophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-benzoyl-1-methyl-6-indolamine hydrochloride

---

Produced as in example 157 by reaction of 3-[3-(4-cyanophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-benzoyl-1-methyl-6-indolamine with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 99% of theory
Melting point: 138°C
$C_{30}H_{30}N_4O_4$ (510.60)

Example 168

3-[3-(4-amidinophenyl)-propionyl]-N-hydroxycarbonylmethyl-N-benzoyl-1-methyl-6-indolamine hydrochloride

---

Produced as in example 2 by saponification of 3-[3-(4-amidinophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-benzoyl-1-methyl-6-indolamine hydrochloride.
Yield: 92% of theory
Melting point: 188°C (decomp.)
$C_{28}H_{26}N_4O_4$ (482.54)

Example 169

3-[3-(4-amidinophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-[(2-methoxycarbonyl)-phenylcarbonyl]-1-methyl-6-indolamine hydrochloride

---

Produced as in example 157 by reaction of 3-[3-(4-cyanophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-[(2-methoxycarbonyl)-phenylcarbonyl]-1-methyl-6-indolamine with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 58% of theory
R_f value: 0.66 (silica gel; dichloromethane/methanol = 4:1)
Melting point: 96°C
$C_{32}H_{32}N_4O_6$ (568.64)

Example 170

3-[3-(4-amidinophenyl)-propionyl]-N-hydroxycarbonylmethyl-N-[(2-hydroxycarbonyl)-phenylcarbonyl]-1-methyl-6-indolamine hydrochloride

---

Produced as in example 2 by saponification of 3-[3-(4-amidinophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-[(2-methoxycarbonyl)-phenylcarbonyl]-1-methyl-6-indolamine hydrochloride.
Yield: 41% of theory
$C_{29}H_{26}N_4O_6$ (526.55)
Mass spectrum: $(M+H)^+ = 527$

Example 171

3-[3-(4-amidinophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-(2-pyridylcarbonyl)-1-methyl-6-indolamine hydrochloride

---

Produced as in example 157 by reaction of 3-[3-(4-cyanophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-(2-pyridylcarbonyl)-1-methyl-6-indolamine with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 18% of theory (deliquescent solid)
$C_{29}H_{29}N_5O_4$ (511.59)
$R_f$value: 0.50 (silica gel; dichloromethane/methanol = 4:1)

Example 172

3-[3-(4-amidinophenyl)-propionyl]-N-hydroxycarbonylmethyl-N-(2-pyridylcarbonyl)-1-methyl-6-indolamine hydrochloride

---

Produced as in example 2 by saponification of 3-[3-(4-amidinophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-(2-pyridylcarbonyl)-1-methyl-6-indolamine hydrochloride.
Yield: 85% of theory
Melting point: 128°C
$C_{27}H_{25}N_5O_4$ (483.53)

Example 173

3-[3-(4-amidinophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-(3-pyridylcarbonyl)-1-methyl-6-indolamine hydrochloride

---

Produced as in example 157 by reaction of 3-[3-(4-cyanophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-(3-pyridylcarbonyl)-1-methyl-6-indolamine with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 55% of theory
Melting point: 69°C
$C_{29}H_{29}N_5O_4$ (511.59)

Example 174

3-[3-(4-amidinophenyl)-propionyl]-N-hydroxycarbonylmethyl-N-(3-pyridylcarbonyl) -1-methyl-6-indolamine hydrochloride

---

Produced as in example 2 by saponification of 3-[3-(4-amidinophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-(3-pyridylcarbonyl) -1-methyl-6-indolamine hydrochloride.
Yield: 92% of theory
Melting point: 138°C (decomp.)
$C_{27}H_{25}N_5O_4$ (483.53)

Example 175

3-[3-(4-amidinophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-(8-quinolinylcarbonyl) -1-methyl-6-indolamine hydrochloride

---

Produced as in example 157 by reaction of 3-[3-(4-cyanophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-(8-quinolinylcarbonyl) -1-methyl-6-indolamine with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 42% of theory
R_f value: 0.53 (silica gel; dichloromethane/methanol = 4:1)
$C_{33}H_{31}N_5O_4$ (561.65)
Mass spectrum: $(M+H)^+ = 562$

Example 176

3-[3-(4-amidinophenyl)-propionyl]-N-hydroxycarbonylmethyl-N-(8-quinolinylcarbonyl) -1-methyl-6-indolamine hydrochloride

---

Produced as in example 2 by saponification of 3-[3-(4-amidinophenyl)-propionyl]-N-ethoxycarbonylmethyl-N-(8-quinolinylcarbonyl) -1-methyl-6-indolamine hydrochloride.
Yield: 84% of theory
$C_{31}H_{27}N_5O_4$ (533.59)
Mass spectrum: $(M+H)^+ = 534$

Example 177

3-[3-(4-amidinophenyl)-propionyl]-N-(2-ethoxycarbonylethyl)-N-(3-pyridylcarbonyl) -1-methyl-6-indolamine hydrochloride

---

Produced as in example 157 by reaction of 3-[3-(4-cyanophenyl)-propionyl]-N-(2-ethoxycarbonylethyl)-N-(3-pyridylcarbonyl) -1-methyl-6-indolamine with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 90% of theory
Melting point: 120°C (decomp.)
$C_{30}H_{31}N_5O_4$ (525.61)
Mass spectrum: $(M+H)^+ = 526$

Example 178

3-[3-(4-amidinophenyl)-propionyl]-N-(2-ethoxycarbonylethyl)-N-(3-pyridylcarbonyl) -1-methyl-6-indolamine hydrochloride

---

Produced as in example 2 by saponification of 3-[3-(4-amidinophenyl)-propionyl]-N-(2-ethoxycarbonylethyl)-N-(3-pyridylcarbonyl) -1-methyl-6-indolamine hydrochloride.
Yield: 84% of theory
$C_{28}H_{27}N_5O_4$ (497.56)
Mass spectrum: $(M+H)^+ = 498$

Example 179

3-[3-(4-amidinophenyl)-propionyl]-N-butylsulfonyl-1-methyl-6-indolamine hydrochloride

---

Produced as in example 75 by reaction of 3-[3-(4-cyanophenyl)-propionyl]-N-butylsulfonyl-1-methyl-6-indolamine with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 99% of theory
$C_{23}H_{28}N_4O_3S$ (440.57)
Mass spectrum: $(M+H)^+ = 441$

Example 180

3-[3-(4-amidinophenyl)-propionyl]-N-phenylsulfonyl-1-methyl-6-indolamine hydrochloride

---

Produced as in example 75 by reaction of 3-[3-(4-cyanophenyl)-propionyl]-N-phenylsulfonyl-1-methyl-6-indolamine with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 73% of theory
$C_{25}H_{24}N_4O_3S$ (460.56)
Mass spectrum: $(M+H)^+ = 461$

Example 181

3-[3-(4-amidinophenyl)-propionyl]-N-(2,5-dichlorophenylsulfonyl)-1-methyl-6-indolamine hydrochloride

---

Produced as in example 75 by reaction of 3-[3-(4-cyanophenyl)-propionyl]-N-(2,5-dichlorophenylsulfonyl)-1-methyl-6-indolamine with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 99% of theory
Melting point: 192-194°C (decomp.)
$C_{25}H_{22}Cl_2N_4O_3S$ (529.45)
Mass spectrum: $(M+H)^+ = 533.\ 531,\ 529$

Example 182

3-[3-(4-amidinophenyl)-propionyl]-N-(5-isoquinolinylsulfonyl)-1-methyl-6-indolamine hydrochloride

---

Produced as in example 75 by reaction of 3-[3-(4-cyanophenyl)-propionyl]-N-(5-isoquinolinylsulfonyl)-1-methyl-6-indolamine with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 60% of theory
Melting point: starting at 230°C (decomp.)
$C_{28}H_{25}N_5O_3S$ (511.61)
Mass spectrum: $(M+H)^+ = 512$

Example 183

3-[3-(4-amidinophenyl)-propionyl]-N-(8-quinolinylsulfonyl)-1-methyl-6-indolamine hydrochloride

---

Produced as in example 75 by reaction of 3-[3-(4-cyanophenyl)-propionyl]-N-(8-quinolinylsulfonyl)-1-methyl-6-indolamine with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 75% of theory
Melting point: 110°C (decomp.)
$C_{28}H_{25}N_5O_3S$ (511.61)
Mass spectrum: $(M+H)^+ = 512$

Example 184

3-[3-(4-amidinophenyl)-propionyl]-N-(8-quinolinylsulfonyl)-N-ethoxycarbonylmethyl-1-methyl-6-indolamine hydroiodide

---

Produced as in example 79 by reaction of 3-[3-(4-cyanophenyl)-propionyl]-N-(8-quinolinylsulfonyl)-1-methyl-6-indolamine with hydrogen sulfide, methyliodide and ammonium acetate.
Yield: 55% of theory
Melting point: 125°C (decomp.)
$C_{32}H_{31}N_5O_5S$ (597.70)
Mass spectrum: $(M+H)^+ = 598$

Example 185

3-[3-(4-amidinophenyl)-propionyl]-N-(8-quinolinylsulfonyl)-N-hydroxycarbonylmethyl)-1-methyl-6-indolamine hydrochloride

---

Produced as in example 2 by saponification of 3-[3-(4-amidinophenyl)-propionyl]-N-(8-quinolinylsulfonyl)-N-ethoxycarbonylmethyl)-1-methyl-6-indolamine hydroiodide
Yield: 89% of theory
Melting point: starting at 210°C (decomp.)
$C_{30}H_{27}N_5O_5S$ (569.64)
Mass spectrum: $(M+H)^+ = 570$

Example 186

3-{3-[4-(N-methoxycarbonyl)-amidinophenyl]-propionyl}-N-(8-quinolinylsulfonyl)-N-ethoxycarbonylmethyl-1-methyl-6-indolamine

---

Produced as in example 108 from 3-[3-(4-amidinophenyl)-propionyl]-N-(8-quinolinylsulfonyl)-N-ethoxycarbonylmethyl-1-methyl-6-indolamine hydroiodide and chloroformic acid methylester.
Yield: 78% of theory
Melting point: starting at 90°C (decomp.)
$C_{34}H_{33}N_5O_7S$ (655.74)
Mass spectrum: $(M+H)^+ = 656$

Example 187

3-{3-[4-(N-benzyloxycarbonyl)-amidinophenyl]-propionyl}-N-(8-quinolinylsulfonyl)-N-ethoxycarbonylmethyl-1-methyl-6-indolamine

---

Produced as in example 108 from 3-[3-(4-amidinophenyl)-propionyl]-N-(8-quinolinylsulfonyl)-N-ethoxycarbonylmethyl-1-methyl-6-indolamine hydroiodide and chloroformic acid benzylester.
Yield: 69% of theory
Melting point: starting at 96°C (decomp.)
$C_{40}H_{37}N_5O_7S$ (731.83)
Mass spectrum: $(M+H)^+ = 732$

Example 188

3-[3-(4-amidinophenyl)-propionyl]-N-(8-quinolinylsulfonyl)-N-(2-ethoxycarbonylethyl)-1-methyl-6-indolamine hydrochloride

---

Produced as in example 76 by reaction of 3-[3-(4-cyanophenyl)-propionyl]-N-(8-quinolinylsulfonyl)-N-(2-ethoxycarbonylethyl)-1-methyl-6-indolamine with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 83% of theory
R_f value: 0.20 (silica gel; dichloromethane/ethanol = 17:3)
$C_{33}H_{33}N_5O_5S$ (611.73)
Mass spectrum: $(M+H)^+ = 612$

Example 189

3-[3-(4-amidinophenyl)-propionyl]-N-(8-quinolinylsulfonyl)-N-(2-hydroxycarbonylethyl)-1-methyl-6-indolamine hydrochloride

---

Produced as in example 2 by saponification of 3-[3-(4-amidinophenyl)-propionyl]-N-(8-quinolinylsulfonyl)-N-(2-ethoxycarbonylethyl)-1-methyl-6-indolamine hydrochloride.
Yield: 80% of theory
Melting point: starting at 180°C
$C_{31}H_{29}N_5O_5S$ (583.67)
Mass spectrum: $(M+H)^+ = 584$

Example 190

3-(4-amidinophenylmethylaminocarbonyl)-N-(8-quinolinylsulfonyl)-1-methyl-6-indolamine hydrochloride

---

a) 1-methyl-6-nitroindole-3-carboxylic acid methylester

51 g (0.33 mol) potassium permanganate are added in portions at room temperature to a solution of 51.0 g (0.25 mol) of a mixture made up of 5- and 6-nitro-1-methyl-3-indolaldehyde and 8.1 g (25 mmol) tetrabutylammoniumbromide in 1 liter of pyridine. After 1 hour of stirring the solvent is removed *in vacuo*, the residue is mixed with 1N caustic soda solution and washed with ethyl acetate and dichloromethane. The aqueous phase is then acidified with semi-concentrated hydrochloric acid, and the preciptated product is drawn off and washed with water, isopropanol and ethyl acetate. This raw product (26 g) is suspended in 350 ml methanol and mixed with 17.5 ml (0.24 mol) thionyl chloride at -30°C. The mixture is stirred for 2 hours at -30°C and for 3 hours at room temperature. 10 ml concentrated sulfuric acid are then added and the mixture is heated for 18 hours to reflux. Ice water is then added, and extraction is

performed with dichloromethane/methanol (10:1). The solvent is removed *in vacuo* and the residue obtained is chromatographed on silica gel (cyclohexane/ethyl acetate = 3: 2).
Yield: 3.6 g (13% of theory)
$C_{11}H_{16}N_2O_4$ (234.2)
Melting point: 207°C
Calculated: C 56.41 H 4.30 N 11.96
Found: C 56.22 H 4.35 N 11.94

b) 1-methyl-6-nitroindole-3-carboxylic acid

3.60 g (15.3 mmol) 1-methyl-6-nitroindole-3-carboxylic acid methylester are dissolved in 50 ml ethanol and stirred with 20 ml 4N caustic soda solution at 80°C for one hour. After the mixture has cooled to room temperature, 40 ml 4N hydrochloric acid are added. The precipitate is drawn off, washed with water, isopropanol and ether, and dried.
Yield: 3.3 g (92% of theory)
Melting point: 291°C (decomp.)

c) 1-methyl-6-nitroindole-3-carboxylic acid-(4-cyanophenylmethyl)-amide

Produced as in example 124a from 1-methyl-6-nitroindole-3-carboxylic acid, 4-cyanobenzylamine, TBTU and HOBt.
Yield: 97% of theory
$C_{18}H_{14}N_4O_3$ (334.3)
Melting point: 262°C
Calculated: C 64.67 H 4.22 N 16.76
Found: C 64.43 H 4.43 N 16.80

d) 6-amino-1-methylindole-3-carboxylic acid-(4-cyanophenylmethyl)-amide

Produced as in example 124b by catalytic hydration of 1-methyl-6-nitroindole-3-carboxylic acid-(4-cyanophenylmethyl)-amide.
Yield: 92% of theory
$C_{18}H_{16}N_4O$ (304.4)
Melting point: 206°C
Calculated: C 71.04 H 5.30 N 18.41
Found: C 70.55 H 5.46 N 18.00

e) 3-(4-cyanophenylmethylaminocarbonyl)-N-(8-quinolinylsulfonyl)-1-methyl-6-indolamine

Produced as in example 124c from 6-amino-1-methylindole-3-carboxylic acid-(4-cyanophenylmethyl)-amide and quinoline-8-sulfonic acid chloride.
Yield: 76% of theory
Melting point: 272°C

f) 3-(4-amidinophenylmethylaminocarbonyl)-N-(8-quinolinylsulfonyl)-1-methyl-6-indolamine hydrochloride

Produced as in example 124d by reaction of 3-(4-cyanophenylmethylamino-carbonyl)-N-(8-quinolinylsulfonyl)-1-methyl-6-indolamine with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 90% of theory
Melting point: 215°C (decomp.)
$C_{27}H_{24}N_6O_3S$ (512.60)
Mass spectrum: $(M+H)^+ = 513$

Example 191

3-(4-amidinophenylmethylaminocarbonyl)-N-(8-quinolinylsulfonyl)-N-ethoxycarbonylmethyl-1-methyl-6-indolamine hydrochloride

---

Produced as in example 130 by reaction of of 3-(4-cyanophenylmethylamino-carbonyl)-N-(8-quinolinylsulfonyl)-N-ethoxycarbonylmethyl-1-methyl-6-indolamine with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 79% of theory
Melting point: 170°C (decomp.)
$C_{31}H_{30}N_6O_5S$ (598.69)
Mass spectrum: $(M+H)^+ = 599$

Example 192

3-(4-amidinophenylmethylaminocarbonyl)-N-(8-quinolinylsulfonyl)-N-hydroxycarbonylmethyl-1-methyl-6-indolamine

---

Produced as in example 128 by saponificationof of 3-(4-amidinophenylmethylaminocarbonyl)-N-(8-quinolinylsulfonyl)-N-ethoxycarbonylmethyl-1-methyl-6-indolamine hydrochloride..
Yield: 85% of theory
Melting point: 240°C (decomp.)
$C_{29}H_{26}N_6O_5S$ (570.63)
Mass spectrum: $(M+H)^+ = 571$

Example 193

3-(4-amidinophenylacetyl)-5-bromo-1-methylindole hydrochloride

---

a) 5-bromo-1-methylindole

Produced as in example 1a from 5-bromoindole and methyliodide.
Yield: 99% of theory

b) 3-(4-cyanophenylacetyl)-5-bromo-1-methylindole

Produced as in example 136 by Friedel-Crafts acylation of 5-bromo-1-methylindole with 4-cyanophenylacetic acid chloride.
Yield: 26% of theory
Melting point: 190-191°C

c) 3-(4-amidinophenylacetyl)-5-bromo-1-methylindole hydrochloride

Produced as in example 1g by reaction of 3-(4-cyanophenylacetyl)-5-bromo-1-methylindole with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 63% of theory
Melting point: 246°C (decomp.)
$C_{18}H_{16}BrN_3O$ (370.25)
Mass spectrum: $(M+H)^+$ = 372, 370

Example194

3-(4-amidinophenylacetyl)-N-ethoxycarbonylmethyl-N-(2-pyridylcarbonyl)-1-methyl-6-indolamine hydrochloride

---

a) 6-nitroindole-3-carboxylic acid methylester

500 ml concentrated nitric acid are added at 15°C by continuous dripping to a suspension of 100 g (0.57 mol) indole-3-carboxylic acid methylester in 500 ml glacial acetic acid. The mixture is stirred for 6 hours at 4°C and is then allowed to stand at 8°C. The precipitate that forms is drawn off and washed with 50% acetic acid, ethanol and ether.
Yield: 55.5 g (44% of theory)
Melting point: 265°C

b) 6-nitroindole-3-carboxylic acid

Produced as in example 190b by saponification of 6-nitroindole-3-carboxylic acid methylester.
Yield: 99% of theory
Melting point: 273°C

c) 6-nitroindole

49.7 g (241 mmol) 6-nitroindole-3-carboxylic acid and 250 ml quinoline are heated for 2.5 hours to 143°C and then for 0.5 hours to 172°C. After cooling, the reaction solution is poured onto ice and acidified with concentrated hydrochloric acid. The precipitate is drawn off, absorbed in ethyl acetate and washed with water. After concentration by evaporation and drying, the desired compound is obtained.
Yield: 37.0 g (94% of theory)
Melting point: 140-144°C

d) 1-methyl-6-nitroindole

117 ml 50% caustic soda solution and 21.5 ml (342 mmol) methyliodide are added at 15°C to a solution of 37.0 g (228 mmol) 6-nitroindole and 77.5 g (228 mmol) tetrabutylammonium hydrogen sulfate in 250 ml dichloromethane. The solution is stirred vigorously at room temperature for one hour and then washed with water. After removal of the solvent *in vacuo*, it is chromatographed on silica gel (petroleum ether/ethyl acetate = 2:1).
Yield: 37.9 g (94% of theory)
Melting point: 80-82°C

e) 3-(4-cyanophenylacetyl)-1-methyl-6-nitroindole

Produced as in example 136a by Friedel-Crafts acylation of 1-methyl-6-nitroindole with 4-cyanophenylacetic acid chloride.
Yield: 44% of theory
Melting point: 235°C

f) 3-(4-cyanophenylacetyl)-1-methyl-6-indolamine

Produced as in example 136b by catalytic hydrationof 3-(4-cyanophenylacetyl)-1-methyl-6-nitroindole.
Yield: 62% of theory
Melting point: 185-190°C

g) 3-(4-cyanophenylacetyl)-N-ethoxycarbonylmethyl-1-methyl-6-indolamine

Produced as in example 136c by alkylation of 3-(4-cyanophenylacetyl)-1-methyl-6-indolamine with iodoacetic acid ethylester.
Yield: 93% of theory
Melting point: 140-145°C

h) 3-(4-cyanophenylacetyl)-N-ethoxycarbonylmethyl-N-(2-pyridylcarbonyl)-1-methyl-6-indolamine

Produced as in example 136d from 3-(4-cyanophenylacetyl)-N-ethoxycarbonylmethyl-1-methyl-6-indolamine and pyridine-2-carboxylic acid chloride
Yield: 61% of theory
Melting point: 148-150°C

i) 3-(4-amidinophenylacetyl)-N-ethoxycarbonylmethyl-N-(2-pyridylcarbonyl)-1-methyl-6-indolamine hydrochloride

Produced as in example 136e by reaction of 3-(4-cyanophenylacetyl)-N-ethoxycarbonylmethyl-N-(2-pyridylcarbonyl)-1-methyl-6-indolamine with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 75% of theory
Melting point: 160°C
$C_{28}H_{27}H_5O_4$ (497.56)
Mass spectrum: $(M+H)^+ = 498$

Example 195

3-(4-amidinophenylacetyl)-N-hydroxycarbonylmethyl-N-(2-pyridylcarbonyl)-1-methyl-6-indolamine

---

Produced as in example 128 by saponification of 3-(4-amidinophenylacetyl)-N-ethoxycarbonylmethyl-N-(2-pyridylcarbonyl)-1-methyl-6-indolamine hydrochloride.
Yield: 75% of theory
Melting point: 242°C
$C_{26}H_{23}H_5O_4$ (469.50)
Mass spectrum: $(M+H)^+ = 470$

Example 196

3-(4-amidinophenylacetyl)-N-ethoxycarbonylmethyl-N-(3-pyridylcarbonyl)-1-methyl-6-indolamine hydrochloride

---

Produced as in example 194 by reaction of 3-(4-cyanophenylacetyl)-N-ethoxycarbonylmethyl-N-(3-pyridylcarbonyl)-1-methyl-6-indolamine with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 72% of theory
Melting point: starting at 120°C
$C_{28}H_{27}H_5O_4$ (497.56)
Mass spectrum: $(M+H)^+ = 498$

Example 197

3-(4-amidinophenylacetyl)-N-hydroxycarbonylmethyl-N-(3-pyridylcarbonyl)-1-methyl-6-indolamine

---

Produced as in example 128 by saponification of 3-(4-amidinophenylacetyl)-N-ethoxycarbonylmethyl-N-(3-pyridylcarbonyl)-1-methyl-6-indolamine hydrochloride.
Yield: 81% of theory
Melting point: 238°C
$C_{26}H_{23}H_5O_4$ (469.50)
Mass spectrum: $(M+H)^+ = 470$

Example 198

3-(4-amidinophenylacetyl)-N-ethoxycarbonylmethyl-N-(1-methyl-3-pyridiniocarbonyl)-1-methyl-6-indolamine-iodide hydrochloride

---

a) 3-(4-cyanophenylacetyl)-N-ethoxycarbonylmethyl-N-(1-methyl-3-pyridiniocarbonyl)-1-methyl-6-indolamine-iodide

A solution of 960 mg (2.0 mmol) 3-(4-cyanophenylacetyl)-N-ethoxycarbonylmethyl-N-(3-pyridylcarbonyl)-1-methyl-6-indolamine in 20 ml acetonitrile is mixed with 0.38 ml (6.0 mmol) methyliodide. The mixture is heated for 4 hours to 60°C. The solvent is then removed *in vacuo* and the residue is triturated with ether.
Yield: 1.2 g (99% of theory)
Melting point: 215°C

b) 3-(4-amidinophenylacetyl)-N-ethoxycarbonylmethyl-N-(1-methyl-3-pyridiniocarbonyl)-1-methyl-6-indolamine-iodide hydrochloride

Produced as in example 194 by reaction of 3-(4-cyanophenylacetyl)-N-ethoxycarbonylmethyl-N-(1-methyl-3-pyridiniocarbonyl)-1-methyl-6-indolamine iodide with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 46% of theory
Melting point: 180°C
$C_{29}H_{30}N_5O_4$ (512.27)
Mass spectrum: $(M+H)^+ = 512$

Example 199

3-(4-amidinophenylacetyl)-N-(8-quinolinylcarbonyl)-1-methyl-6-indolamine hydrochloride

---

Produced as in examples 75 and 194 by reaction of 3-(4-cyanophenylacetyl)-N-(8-quinolinylcarbonyl)-1-methyl-6-indolamine with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 68% of theory
Melting point: 200°C
$C_{27}H_{23}N_5O_3S$ (497.58)
Mass spectrum: $(M+H)^+ = 498$

Example 200

3-(4-amidinophenylacetyl)-N-ethoxycarbonylmethyl-N-(8-quinolinylcarbonyl)-1-methyl-6-indolamine hydrochloride

---

Produced as in examples 75 and 194 by reaction of 3-(4-cyanophenylacetyl)-N-ethoxycarbonylmethyl-N-(8-quinolinylcarbonyl)-1-methyl-6-indolamine with ethanolic hydrochloric acid and ammonium carbonate.

Yield: 40% of theory
Melting point: 160°C (decomp.)
$C_{31}H_{29}N_5O_5S$ (583.67)
Mass spectrum: $(M+H)^+ = 584$

Example 201

3-[2-(4-amidinophenyl)-3-ethoxycarbonylpropionyl]-N-ethoxycarbonylmethyl-N-(8-quinolinylcarbonyl)-1-methyl-6-indolamine hydrochloride

---

a) 3-[2-(4-cyanophenyl)-3-ethoxycarbonylpropionyl]-N-ethoxycarbonylmethyl-N-(8-quinolinylcarbonyl)-1-methyl-6-indolamine

A solution of 1.27 g (2.64 mmol) 3-(4-cyanophenylacetyl)-N-(8-quinolinylcarbonyl)-1-methyl-6-indolamine in 50 ml acetone is mixed with 1.37 g (9.89 mmol) potassium carbonate and 0.44 ml (3.96 mmol) bromoacetic acid ethylester. The mixture is stirred for 24 hours at room temperature, then filtered off from the insoluble part. The residue is concentrated to dryness and then chromatographed on silica gel (ethyl acetate/petroleum ether = 2:1).
Yield: 41% of theory
Melting point: 225-230°C
Mass spectrum: $(M+H)^+ = 652$

b) 3-[2-(4-amidinophenyl)-3-ethoxycarbonylpropionyl]-N-ethoxycarbonylmethyl-N-(8-quinolinylcarbonyl)-1-methyl-6-indolamine hydrochloride

Produced as in example 194 by reaction of 3-[2-(4-cyanophenyl)-3-ethoxycarbonylpropionyl]-N-ethoxycarbonylmethyl-N-(8-quinolinylcarbonyl)-1-methyl-6-indolamine with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 60% of theory
Melting point: 185°C (decomp.)
$C_{35}H_{35}N_5O_7S$ (669.76)
Mass spectrum: $(M+H)^+ = 670$

Example 202

3-(4-amidinophenylacetyl)-N-hydroxycarbonylmethyl-N-(8-quinolinylcarbonyl)-1-methyl-6-indolamine

---

Produced as in example 128 by saponification of 3-(4-amidinophenylacetyl)-N-ethoxycarbonylmethyl-N-(8-quinolinylcarbonyl)-1-methyl-6-indolamine hydrochloride.
Yield: 84% of theory

Melting point: 235°C
$C_{29}H_{25}N_5O_5S$ (555.62)
Mass spectrum: $(M+H)^+ = 556$

Example 203

3-[3-(4-amidinophenyl)-propionyl]-N-(8-quinolinylcarbonyl)-1-methyl-5-indolamine dihydrochloride

---

Produced as in examples 1, 49 and 75 by reaction of 3-[3-(4-cyanophenyl)-propionyl]-N-(8-quinolinylcarbonyl)-1-methyl-5-indolamine with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 28% of theory
R_f value: 0.29 (silica gel; dichloromethane/methanol = 9:1)
$C_{29}H_{27}N_5O_3S$ (525.63)
Mass spectrum: $(M+H)^+ = 526$

Example 204

3-[3-(4-amidinophenyl)-propionyl]-N-(8-quinolinylcarbonyl)-1-propyl-5-indolamine

---

Produced as in examples 1, 49 and 75 by reaction of 3-[3-(4-cyanophenyl)-propionyl]-N-(8-quinolinylcarbonyl)-1-propyl-5-indolamine with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 13% of theory
R_f value: 0.60 (silica gel; dichloromethane/methanol = 5:1)
$C_{30}H_{29}N_5O_3S$ (539.66)
Mass spectrum: $(M+H)^+ = 540$

Example 205

3-[3-(4-amidinophenyl)-propionyl]-N-phenylsulfonyl-1-ethoxycarbonylmethyl-5-indolamine hydrochloride

---

Produced as in examples 1, 49 and 75 by reaction of 3-[3-(4-cyanophenyl)-propionyl]-N-phenylsulfonyl-1-ethoxycarbonylmethyl-5-indolamine with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 56% of theory
Melting point: 214-215°C
$C_{28}H_{28}N_4O_5S$ (532.62)
Mass spectrum: $(M+H)^+ = 533$

Example 206

3-[3-(4-amidinophenyl)-propionyl]-N-phenylsulfonyl-1-hydroxycarbonylmethyl-5-indolamine hydrochloride

---

Produced as in example 2 by saponification of 3-[3-(4-amidinophenyl)-propionyl]-N-phenylsulfonyl-1-ethoxycarbonylmethyl-5-indolamine hydrochloride.
Yield: 99% of theory
Melting point: >260°C
$C_{26}H_{24}N_4O_5S$ (504.57)
Mass spectrum: $(M+H)^+ = 505$

Example 207

3-[3-(4-amidinophenyl)-propionyl]-N-phenylsulfonyl-N-(2-dimethylaminoethyl)-1-ethoxycarbonylmethyl-5-indolamine dihydrochloride

---

Produced as in examples 1, 49 and 75 by reaction of 3-[3-(4-cyanophenyl)-propionyl]-N-phenylsulfonyl-N-(2-dimethylaminoethyl)-1-ethoxycarbonylmethyl-5-indolamine with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 50% of theory
Melting point: 210°C (decomp.)
$C_{32}H_{37}N_5O_5S$ (603.75)
Mass spectrum: $(M+H)^+ = 604$

Example 208

3-[3-(4-amidinophenyl)-propionyl]-N-phenylsulfonyl-N- (2-dimethylaminoethyl)-1-hydroxycarbonylmethyl-5-indolamine dihydrochloride

---

Produced as in example 2 by saponification of 3-[3-(4-amidinophenyl)-propionyl]-N-phenylsulfonyl-N-(2-dimethylaminoethyl-1-ethoxycarbonylmethyl-5-indolamine dihydrochloride.
Yield: 63% of theory
Melting point: 268°C (decomp.)
$C_{30}H_{33}N_5O_5S$ (575.69)
Mass spectrum: $(M+H)^+ = 576$

Example 209

1-[3-(4-amidinophenyl)-propyl]-N-phenylsulfonyl-5-indolamine hydrochloride

---

a) 4-(3-hydroxypropyl)benzonitrile

28.6 ml (0.30 mol) chloroformic acid ethylester are added at -20°C under nitrogen to a solution of 52.5 g (0.30 mol) 3-(4-cyanophenyl)-propionic acid (example 1b) and 42 ml (0.30 mol) triethylamine in 600 ml THF. After 1.5 hours of stirring at -20°C, the solution is drawn off from the insoluble part and the filtrate is added in drops at 0°C to a solution of 34 g (0.90 mol) sodium boron hydride and 600 ml water/methanol (3:1). The mixture is stirred for another hour at room temperature, then diluted with water and acidified with glacial acetic acid. After extraction with ethyl acetate and concentration, the desired compound is obtained.
Yield: 42.3 g (88% of theory; oil).

b) 4-(3-iodopropyl)-benzonitrile

81 ml (1.3 m [sic]l) methyliodide are added at room temperature to a solution of 42.2 ml (0.26 ml [sic]) CDI and 42 ml (0.26 ml [sic]) 4-(3-hydroxypropyl)-benzonitrile. The mixture is stirred for an hour at room temperature and then heated for 1.5 hours to reflux. After cooling, 200 ml water and 400 ml ether are added. The organic phase is separated and washed with 2N hydrochloric acid, saturated sodium hydrogen carbonate solution, 10% sodium thiosulfate solution and water. After concentration and chromatography on silica gel (cyclohexane/ethyl acetate = 2:1), the desired product is obtained.
Yield: 51.3 ml (73% of theory; oily product)
$C_{10}H_{10}IN$ (271.09)
Calculated: C 44.43 H 3.76 N 5.17
Found: C 44.44 H 3.79 N 5.20

c) 1-[3-(4-cyanophenyl)-propyl]-5-nitroindole

0.48 ml (10 mmol) sodium hydride (55% in paraffin) is added at room temperature in portions over a period of one hour to a solution of 1.6 ml (10 mmol) 5-nitroindole in 20 ml DMSO. 2.7 ml (10 mmol) 4-(3-iodopropyl)-benzonitrile are then added in drops and the solution is stirred for one hour at room temperature. The solution is poured onto ice and extracted with dichloromethane. After removal of the solvent *in vacuo* and trituration with petroleum/ether (5:1), the desired compound is obtained.
Yield: 0.9 ml (30% of theory)

d) 1-[3-(4-cyanophenyl)-propyl]-5-indolamine

Produced as in example 49c by catalytic hydration of 1-[3-(4-cyanophenyl)-propyl]-5-nitroindole.
Yield: 99% of theory

e) 1-[3-(4-cyanophenyl)-propyl]-N-phenylsulfonyl-5-indolamine

Produced as in example 75a from 1-[3-(4-cyanophenyl)-propyl]-5-indolamine and benzene-sulfonic acid chloride.
Yield: 55% of theory.

f) 1-[3-(4-amidinophenyl)-propyl]-N-phenylsulfonyl-5-indolamine hydrochloride

Produced as in example 75b by reaction of 1-[3-(4-cyanophenyl)-propyl]-N-phenylsulfonyl-5-indolamine with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 6% of theory
Melting point: starting at 117°C (decomp.)
$C_{24}H_{24}N_4O_2S$ (432.55)
Mass spectrum: $(M+H)^+ = 433$

Example 210

1-[(4-amidinophenyl)-aminocarbonylmethyl]-N-(8-quinolinylsulfonyl)-5-indolamine hydroiodide

---

a) 1-(ethoxycarbonylmethyl)-5-nitroindole

Produced as in example 1 from 5-nitroindole, bromoacetic acid ethylester and potassium tert. butylate.
Yield: 81% of theory
R_f value: 0.42 (silica gel; dichloromethane/cyclohexane = 4:1)

b) 1-(hydroxycarbonylmethyl)-5-nitroindole

Produced as in example 128 by saponification of 1-(ethoxycarbonylmethyl)-5-nitroindole.
Yield: 85% of theory.

c) 1-[(4-cyanophenyl)-aminocarbonylmethyl]-5-nitroindole

8.2 ml (50.2 mmol) CDI are added to a solution of 9.3 ml (42.2 mmol) 1-(hydroxycarbonylmethyl)-5-nitroindole in 100 ml THF and 20 ml DMF and stirred for an hour at room temperature. 5.9 ml (50.2 mmol) 4-aminobenzonitrile are then added and stirred for 16 hours at room temperature. The solvent is removed *in vacuo*, and the solution is absorbed in dichloromethane and washed with water. After drying over sodium sulfate and concentration, the desired compound is obtained.
Yield: 4.8 ml (35% of theory)

d) 1-[(4-cyanophenyl)-aminocarbonylmethyl]-5-indolamine

Produced as in example 49c by catalytic hydration of 1-[(4-cyanophenyl)-aminocarbonylmethyl]-5-nitroindole.

Yield: 96% of theory

e) 1-[(4-cyanophenyl)-aminocarbonylmethyl]-N-(8-quinolinylsulfonyl)-5-indolamine

Produced as in example 75a from 1-[(4-cyanophenyl)-aminocarbonylmethyl]-5-indolamine and 8-quinoline-sulfonic acid chloride.
Yield: 50% of theory

f) 1-[(4-amidinophenyl)-aminocarbonylmethyl]-N-(8-quinolinylsulfonyl)-5-indolamine hydroiodide

Produced as in example 21 from 1-[(4-cyanophenyl)-aminocarbonylmethyl]-N-(quinolinylsulfonyl)-5-indolamine with hydrogen sulfide, methyliodide and ammonium acetate.
Yield: 54% of theory
R_f value: 0.11 (silica gel; dichloromethane/methanol = 9:1)
$C_{26}H_{22}N_6O_3S$ (498.57)
Mass spectrum: $(M+H)^+ = 499$

Example 211

1-[(4-amidinophenyl)-methyl]-2,3-dimethyl-N-phenylsulfonyl-5-indolamine-hydrochloride

---

a) 1-[(4-cyanophenyl)-methyl]-2,3-dimethyl-5-nitroindole

Produced as in example 209c from 2,3-dimethyl-5-nitroindole, sodium hydride and 4-cyanobenzyl bromide in DMF.
Yield: 87% of theory
$C_{18}H_{15}N_3O_2$ (305.34)
Melting point: 204-206°C
Calculated: C 70.81 H 4.95 N 13.76
Found: C 70.54 H 4.92 N 13.72

b) 1-[(4-cyanophenyl)-methyl]-2,3-dimethyl-5-indolamine

Produced as in example 209d by catalytic hydration of 1-[(4-cyanophenyl)-methyl]-2,3-dimethyl-5-nitroindole.
Yield: 99% of theory

c) 1-[(4-cyanophenyl)-methyl]-2,3-dimethyl-N-phenylsulfonyl-5-indolamine

Produced as in example 209e from 1-[(4-cyanophenyl)-methyl]-2,3-dimethyl-5-indolamine and benzene-sulfonic acid chloride.
Yield: 81% of theory

d) 1-[(4-amidinophenyl)-methyl]-2,3-dimethyl-N-phenylsulfonyl-5-indolamine hydrochloride

Produced as in example 209f by reaction of 1-[(4-cyanophenyl)-methyl]-2,3-dimethyl-N-phenylsulfonyl-5-indolamine with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 43% of theory
$C_{24}H_{24}N_4O_2S \times HCl \times H_2O$ (487.03)
Melting point: 200-210°C (decomp.)
Calculated: C 59.19 H 5.59 N 11.50 S 6.58
Found: C 59.51 H 5.55 N 11.33 S 6.35

Example 212

1-[3-(4-amidinophenyl)-propyl]-2,3-dimethyl-N-phenylsulfonyl-5-indolamine hydroiodide

---

Produced as in examples 209 and 21 from 1-[3-(4-cyanophenyl)-propyl]-2,3-dimethyl-N-phenylsulfonyl-5-indolamine with hydrogen sulfide, methyliodide and ammonium acetate.
Yield: 34% of theory
Melting point: starting at 118°C (decomp.)
$C_{26}H_{28}N_4O_2S$ (460.60)

Example 213

1-[3-(4-amidinophenyl)-propyl]-2,3-dimethyl-N-(8-quinolinylsulfonyl)-5-indolamine hydroiodide

---

Produced as in example 212 from 1-[3-(4-cyanophenyl)-propyl]-2,3-dimethyl-N-(8-quinolinylsulfonyl)-5-indolamine with hydrogen sulfide, methyliodide and ammonium acetate.
Yield: 5% of theory
Melting point: 108°C (decomp.)
$C_{29}H_{29}N_5O_2S$ (511.65)
Mass spectrum: $(M+H)^+ = 512$

Example 214

1-[3-(4-amidinophenyl)-propyl]-N-(8-quinolinylsulfonyl)-N-methoxycarbonylmethyl-2,3-dimethyl-5-indolamine hydroiodide

---

Produced as in example 212 from 1-[3-(4-cyanophenyl)-propyl]-N-(8-quinolinylsulfonyl)-N-methoxycarbonylmethyl-2,3-dimethyl-5-indolamine with hydrogen sulfide, methyliodide and ammonium acetate.

Yield: 2% of theory
Melting point: 110°C (decomp.)
$C_{32}H_{33}N_5O_4S$ (583.72)
Mass spectrum: $(M+H)^+ = 584$

Example 215

1-[3-(4-amidinophenyl)-propyl]-N-(8-quinolinylsulfonyl)-2,3-dimethyl-5-indolamine hydroiodide

a) 1-[3-(4-cyanophenyl)-propionyl]-2,3-dimethyl-5-nitroindole

2.15 ml (54 mmol) powdered sodium hydroxide and 6.5 ml (34 mmol) 3-(4-cyanophenyl)-propionic acid chloride are added at room temperature to a solution of 4.4 ml (23 mmol) 2,3-dimethylindole and 80 mg (0.23 mmol) tetrabutylammonium hydrogen sulfate in 280 ml dichloromethane. The mixture is then stirred for 1.5 hours. The reaction solution is poured into ice water and extracted with dichloromethane. After removal of the solvent *in vacuo*, the desired compound is obtained.
Yield: 4.4 ml (55% of theory)

b) 1-[3-(4-cyanophenyl)-propionyl]-2,3-dimethyl-5-indolamine

Produced as in example 209d by catalytic hydration of 1-[3-(4-cyanophenyl)-propionyl]-2,3-dimethyl-5-nitroindole.

Yield: 80% of theory

c) 1-[3-(4-cyanophenyl)-propionyl]-N-(8-quinolinylsulfonyl)-2,3-dimethyl-5-indolamine

Produced as in example 209e from 1-[3-(4-cyanophenyl)-propionyl]-2,3-dimethyl-5-indolamine and 8-quinoline-sulfonic acid chloride.
Yield: 60% of theory

d) 1-[3-(4-amidinophenyl)-propyl]-N-(8-quinolinylsulfonyl)-2,3-dimethyl-5-indolamine hydroiodide

Produced as in example 212 from 1-[3-(4-cyanophenyl)-propionyl]-N-(8-quinolinylsulfonyl)-2,3-dimethyl-5-indolamine with hydrogen sulfide, methyliodide and ammonium acetate.
Yield: 3% of theory
Melting point: 172°C
$C_{29}H_{27}N_5O_3S$ (525.63)
Mass spectrum: $(M+H)^+ = 526$

Example 216

1-[3-(4-amidinophenyl)-propyl]-N-(8-quinolinylsulfonyl)-N-ethoxycarbonylmethyl-2,3-dimethyl-5-indolamine hydroiodide

---

Produced as in example 212 from 1-[3-(4-cyanophenyl)-propyl]-N-(8-quinolinylsulfonyl)-N-ethoxycarbonylmethyl-2,3-dimethyl-5-indolamine with hydrogen sulfide, methyliodide and ammonium acetate.
Yield: 25% of theory
Melting point: 110°C (decomp.)
$C_{33}H_{33}N_5O_5S$ (611.73)

Example 217

Dry ampoule with 75 mg active substance per 10 ml

Composition:

Active substance		75.0 mg
Mannitol		50.0 mg
Water for injection purposes	ad	10.0 ml

Production:
The active substance and mannitol are dissolved in water. Lyophilization after filling. Water for injection purposes is used to dissolve for a ready-to-use solution.

Example 218

Dry ampoules with 35 mg active substance per 2 ml

Composition:

Active substance		35.0 mg
Mannitol		100.0 mg
Water for injection purposes	ad	2.0 ml

Production:
The active substance and mannitol are dissolved in water. Lyophilization after filling.

Water for injection purposes is used to dissolve for a ready-to-use solution.

Example 219

Tablet with 50 mg active substance

Composition:

(1) Active substance	50.0 mg
(2) Lactose	98.0 mg
(3) Corn starch	50.0 mg
(4) Polyvinylpyrrolidone	15.0 mg
(5) Magnesium stearate	2.0 mg
	215.0 mg

Production:

(1), (2) and (3) are mixed and granulated with an aqueous solution of (4). (5) is mixed into the dried granulate. Tablets are pressed out of this mixture, biplanar with a beveled edge on both sides and scored on one side.
Tablet diameter: 9 mm.

Example 220

Tablet with 350 mg active substance

Composition:

(1) Active substance	350.0 mg
(2) Lactose	136.0 mg
(3) Corn starch	80.0 mg
(4) Polyvinylpyrrolidone	30.0 mg
(5) Magnesium stearate	4.0 mg
	600.0 mg

Production:

(1), (2) and (3) are mixed and granulated with an aqueous solution of (4). (5) is mixed into the dried granulate. Tablets are pressed out of this mixture, biplanar with a beveled edge on both sides and scored on one side.
Tablet diameter: 12 mm.

Example 221

Capsules with 50 mg active substance

Composition:

(1) Active substance	50.0 mg
(2) Corn starch, dried	58.0 mg
(3) Lactose, pulverized	50.0 mg
(4) Magnesium stearate	2.0 mg
	160.0 mg

Production:

(1) is triturated with (3). This trituration is added to the mixture of (2) and (4) with thorough mixing.

This powder mixture is loaded into size 3 hard two-piece gelatine capsules in a capsule-filling machine.

Example 222

Capsules with 350 mg active substance

Composition:

(1) Active substance	350.0 mg
(2) Corn starch, dried	46.0 mg
(3) Lactose, pulverized	30.0 mg
(4) Magnesium stearate	4.0 mg
	430.0 mg

Production:

(1) is triturated with (3). This trituration is added to the mixture of (2) and (4) with thorough mixing.

This powder mixture is loaded into size 0 hard two-piece gelatine capsules in a capsule-filling machine.

Example 223

Suppositories with 100 mg active substance

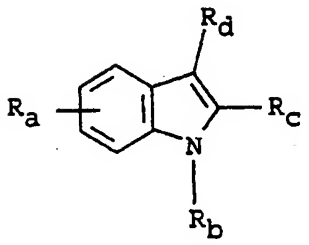
---

1 suppository contains:

Active substance	100.0 mg
Polyethylene glycol (MW 1500)	600.0 mg
Polyethylene glycol (MW. 6000)	460.0 mg
Polyethylene sorbitane monostearate	840.0 mg
	2,000.0 mg

Claims

1. Substituted indoles of the general formula



, (I)

in which

R_a means a fluorine, chlorine or bromine atom, a carboxy, R_3R_4N-CO, R_3R_4N-SO_2 or R_4R_5N group or a group convertible *in vivo* into a carboxy group, in which

R_3 is a hydrogen atom, a C_{1-6}-alkyl, C_{3-7}-cycloalkyl, C_{3-7}-cycloalkyl-C_{1-3}-alkyl or phenyl-C_{1-3}-alkyl group,

an n-C_{2-3}-alkyl group which is substituted in the 2 or 3 position by a C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group,

a phenyl or naphthyl group optionally substituted by a trifluoromethyl group,

a phenyl or naphthyl group monosubstituted or disubstituted by a fluorine, chlorine or bromine atom or by a C_{1-3}-alkyl, C_{1-3}-alkoxy, carboxy-C_{1-3}-alkoxy or carboxy group, the substituents being able to be the same or different,

a phenyl group substituted by three C_{1-3}-alkyl groups or by one amino group and two chlorine or bromine atoms,

a furanyl, thienyl, oxazolyl, thiazolyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl group optionally substituted in the carbon network by a C_{1-3}-alkyl group, to which furanyl, thienyl, oxazolyl, thiazolyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl group a phenyl ring can also be condensed via two carbon atoms in the o position, or one of the aforementioned nitrogen-containing rings in which a nitrogen atom is quarternized by a C_{1-3}-alkylbromide or C_{1-3}-alkyliodide,

R_4 is a hydrogen atom or a C_{1-3}-alkyl group substituted by a carboxy, carboxy-C_{1-3}-alkylamino, di-(carboxy-C_{1-3}-alkyl)-amino, carboxy-C_{1-3}-alkylaminocarbonyl or di-(carboxy-C_{1-3}-alkyl)-aminocarbonyl group, the carboxy groups mentioned above in the definition of the radicals R_3 and R_4 being able to be replaced by a group that is convertible *in vivo* into a carboxy group, or

R_3 and R_4 together with the intervening nitrogen atom are a pyrrolidino, piperidino or hexamethylene imino group,

R_5 is a phenylaminocarbonyl, naphthylaminocarbonyl, R_6CO or R_6SO_2 group in which R_6 has in each case the meanings given above for R_3 except for the hydrogen atom, or

R_4 and R_5 together with the intervening nitrogen atom are an imidazolidine-2,4-dione group substituted by a phenyl group in the 3 position,

one of the radicals R_b or R_d means a C_{1-3}-alkyl group that can be substituted by a carboxy group or a group convertible *in vivo* into a carboxy group, and the other radical of the radicals R_b or R_d means an R_2-A group, in which

A is an n-C_{1-3}-alkylene group which can be substituted by a C_{1-3}-alkyl group optionally substituted by a carboxy group or by a group convertible *in vivo* into a carboxy group, an indole-ring-linked methylene group of the n-C_{1-3}-alkylene group also being able to be replaced by a carbonyl group, or a -CONH-, -CH_2CONH-, -CH_2CH_2CONH-, -CONHCH_2-, -CONCH_2CH_2-, -$COCH_2$O- or -$COCH_2CH_2$O- group, the oxygen atom of the -$COCH_2$O- and -$COCH_2CH_2$O- group being linked in each case to radical R_2, and

R_2 is a phenyl group substituted by the R_1NH-C(=NH) group, in which phenyl group R_1 means a hydrogen atom or an *in vivo* cleavable radical,

and R_c means a hydrogen atom or a C_{1-3}-alkyl group,

and tautomers, stereoisomers, mixtures and salts thereof.

2. Substituted indoles of general formula I in accordance with Claim 1, in which

R_a means a fluorine, chlorine or bromine atom, a carboxy, C_{1-3}-alkoxycarbonyl, R_3R_4N-CO, R_3R_4N-SO_2 or R_4R_5N group, in which

R_3 is a hydrogen atom, a C_{1-6}-alkyl, C_{3-7}-cycloalkyl, C_{3-7}-cycloalkyl-C_{1-3}-alkyl or phenyl-C_{1-3}-alkyl group, an n-C_{2-3}-alkyl group, which is substituted in the 2 or 3 position by a C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group,

a phenyl or naphthyl group,

a phenyl or naphthyl group monosubstituted or disubstituted by a fluorine, chlorine or bromine atom, by a C_{1-3}-alkyl, C_{1-3}-alkoxy, carboxy-C_{1-3}-alkoxy, C_{1-3}-alkoxycarbonyl-C_{1-3}-alkoxy, carboxy, C_{1-3}-alkoxycarbonyl group, the substituents being able to be the same or different,

a phenyl group substituted by three C_{1-3}-alkyl groups or by one amino group and two chlorine or bromine atoms,

a furanyl, thienyl, oxazolyl, thiazolyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl group optionally substituted in the carbon network by a C_{1-3}-alkyl group, to which furanyl, thienyl, oxazolyl, thiazolyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl group a phenyl ring can also be condensed via two carbon atoms in the o position, or one of the aforementioned nitrogen-containing rings in which a nitrogen atom is quarternized by a C_{1-3}-alkylbromide or C_{1-3}-alkyliodide,

R_4 is a hydrogen atom or a C_{1-3}-alkyl group substituted by a carboxy, carboxy-C_{1-3}-alkylamino, di-(carboxy-C_{1-3}-alkyl)-amino, C_{1-3}-alkoxycarbonyl, C_{1-3}-alkoxycarbonyl-C_{1-3}-alkylamino, di-(C_{1-3}-alkoxycarbonyl-C_{1-3}-alkyl)-amino, carboxy-C_{1-3}-alkylaminocarbonyl, di-(carboxy-C_{1-3}-alkyl)-aminocarbonyl, C_{1-3}-alkoxycarbonyl-C_{1-3}-alkylaminocarbonyl or di-(C_{1-3}-alkoxycarbonyl-C_{1-3}-alkyl)-aminocarbonyl group,

R_3 and R_4 together with the intervening nitrogen atom are a pyrrolidino, piperidino or hexamethylene imino group,

R_5 is a phenylaminocarbonyl, naphthylaminocarbonyl, R_6CO or R_6SO_2 group in which R_6 has in each case the meanings given above for R_3 except for the hydrogen atom, or

R_4 and R_5 together with the intervening nitrogen atom are an imidazolidine-2,4-dione group substituted by a phenyl group in the 3 position,

one of the radicals R_b or R_d means a C_{1-3}-alkyl group that can be substituted by a carboxy or C_{1-3}-alkoxycarbonyl group, and the other radical of the radicals R_b or R_d means an R_2-A group, in which

A is an n-C_{1-3}-alkylene group which can be substituted by a C_{1-3}-alkyl group optionally substituted by a carboxy or C_{1-3}-alkoxycarbonyl group, an indole-ring-linked methylene group of the n-C_{1-3}-alkylene group also being able to be replaced by a carbonyl group, or a -CONH-, -CH_2CONH-, -CH_2CH_2CONH-, -CONHCH_2-, -CONCH_2CH_2-, -$COCH_2O$- or -$COCH_2CH_2O$- group, the oxygen atom of the -$COCH_2O$- and -$COCH_2CH_2O$- group being linked in each case to radical R_2, and

R_2 is a phenyl group substituted by the R_1NH-C(=NH) group, in which phenyl group

R_1 means a hydrogen atom or an *in vivo* cleavable radical,

and R_c means a hydrogen atom or a C_{1-3}-alkyl group, and tautomers, stereosiomers and salts thereof.

3. Substituted indoles of general formula I in accordance with Claim 1, in which

R_a in the 5 or 6 position means an R_3R_4N-CO, R_3R_4N-SO_2 or R_4R_5N group, in which

R_3 is a hydrogen atom, a C_{1-6}-alkyl, C_{3-7}-cycloalkyl, C_{3-7}-cycloalkyl-C_{1-3}-alkyl or phenyl-C_{1-3}-alkyl group,

a phenyl or naphthyl group monosubstituted or disubstituted by a fluorine, chlorine or bromine atom, by a C_{1-3}-alkyl, C_{1-3}-alkoxy, carboxy-C_{1-3}-alkoxy, C_{1-3}-alkoxycarbonyl-C_{1-3}-alkoxy, carboxy, C_{1-3}-alkoxycarbonyl group, the substituents being able to be the same or different,

a phenyl group substituted by three C_{1-3}-alkyl groups or by one amino group and two chlorine or bromine atoms,

a furanyl, thienyl, oxazolyl, thiazolyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl group optionally substituted in the carbon network by a C_{1-3}-alkyl group, to which furanyl, thienyl, oxazolyl, thiazolyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl group a phenyl ring can also be condensed via two carbon atoms in the o position, or one of the aforementioned nitrogen-containing rings in which a nitrogen atom is quarternized by a C_{1-3}-alkylbromide or C_{1-3}-alkyliodide,

R_4 is a hydrogen atom or a C_{1-3}-alkyl group substituted by a carboxy, C_{1-3}-alkyloxycarbonyl, carboxy-C_{1-3}-alkylaminocarbonyl, di-(carboxy-C_{1-3}-alkyl)-aminocarbonyl, C_{1-3}-alkoxycarbonyl-C_{1-3}-alkylaminocarbonyl or di-(C_{1-3}-alkoxycarbonyl-C_{1-3}-alkyl)-aminocarbonyl group,

R_3 and R_4 together with the intervening nitrogen atom are a pyrrolidino, piperidino or hexamethylene imino group,

R_5 is an R_6CO or R_6SO_2 group in which R_6 has in each case the meanings given above for R_3 except for the hydrogen atom,

one of the radicals R_b or R_d means a C_{1-3}-alkyl group that can be substituted by a carboxy or C_{1-3}-alkoxycarbonyl group, and the other radical of the radicals R_b or R_d means an R_2-A group, in which

A is an n-C_{1-3}-alkylene group which can be substituted by a C_{1-3}-alkyl group optionally substituted by a carboxy or C_{1-3}-alkoxycarbonyl group, an indole-ring-linked methylene group of the n-C_{1-3}-alkylene group also being able to be replaced by a carbonyl group, or a -CONH-, -CH_2CONH-, -CH_2CH_2CONH-, -CONHCH_2-, -CONCH_2CH_2-, -$COCH_2O$- or -$COCH_2CH_2O$- group, the oxygen atom of the -$COCH_2O$- and -$COCH_2CH_2O$- group being linked in each case to radical R_2, and

R_2 is a phenyl group substituted by the R_1NH-C(=NH) group, in which phenyl group

R_1 means a hydrogen atom or an *in vivo* cleavable radical,

and R_c means a hydrogen atom, and tautomers, stereosiomers and salts thereof.

4. Substituted indoles of general formula I inaccordance with Claim 1, in which

R_a in the 5 position means an R_3R_4N-CO, R_3R_4N-SO_2 or R_4R_5N group, in which

R_3 is a thienyl, thiazolyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl group optionally substituted in the carbon network by methyl group, to which thienyl, thiazolyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl group a phenyl ring can also be condensed via two carbon atoms in the o position,

R_4 is a C_{1-3}-alkyl group substituted by a carboxy, C_{1-3}-alkoxycarbonyl, carboxy-C_{1-3}-alkylaminocarbonyl or C_{1-3}-alkoxycarbonyl-C_{1-3}-alkylaminocarbonyl group,

R_5 is an R_6CO or R_6SO_2 group in which R_6 has in each case the meanings given above for R_3 except for the hydrogen atom,

R_b means a C_{1-3}-alkyl group and

R_d means an R_2A group, in which

A is a -$COCH_2$ or -$COCH_2CH_2$ group and

R_2 is a phenyl group substituted by the R_1NH-C(=NH) group, in which phenyl group

R_1 is a hydrogen atom or a C_{1-3}-alkoxycarbonyl group,

and R_c means a hydrogen atom, and tautomers, stereosiomers and salts thereof.

5. Physiologically compatible salts of the compounds according to Claims 1 through 4, in which R_b or R_d contains an R_1NH-C(=NH)-phenyl group.

6. Drugs containing a compound according to at least one of Claims 1 through 4 in which R_b or R_d contains an R_1NH-C(=NH)-phenyl group or a salt according to Claim 5 in addition optionally to one or more inert vehicles and/or diluents.

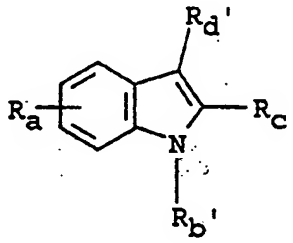
7. Use of a compound according to at least one of Claims 1 through 4 in which R_b or R_d contains an R_1NH-C(=NH)-phenyl group or a salt according to Claim 5 for producing a drug with a thrombin-time extending effect, a thrombin-

inhibiting effect, an inhibiting effect on related serine proteases XII and a fibrinogen-receptor antagonistic effect.

8. Procedure for producing a drug according to Claim 6, characterized in that a compound according to at least one of Claims 1 through 4 in which R_b or R_d contains an R_1NH-C(=NH)-phenyl group or a salt according to Claim 5 is incorporated in a non-chemical manner into one or more inert vehicles and/or diluents.

9. Procedure for producing the compounds according to Claims 1 through 5, characterized in that

a. To produce a compound of general formula I in which R_2 is a phenyl group substituted by the NH_2-C(=NH) group, a compound optionally formed in the reaction mixture of the general formula



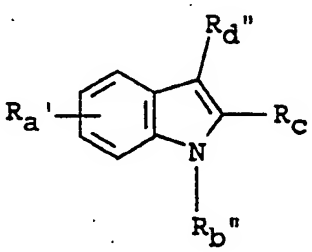
, (II)

in which
R_a and R_c are as defined in Claims 1 through 4,
one of the radicals R_b' or R_d' is a C_{1-3}-alkyl group which can be substituted by a C_{1-3}-alkoxycarbonyl group, and the other radical of radicals R_b' or R_d' is an R_2'-A group in which A is as defined in Claims 1 through 4 and R_2' is a phenyl group substituted by a Z_1-C(=NH) group, in which phenyl group

Z_1 is an alkoxy, aralkoxy, alkylthio or aralkylthio group

is reacted with ammonia or salts thereof, or

b. To produce a compound of general formula I, in which at least one of the radicals R_a, R_b and R_d contains a carboxy group and/or R_b or R_d contain an NH_2-C(=NH) group, a compound of the general formula

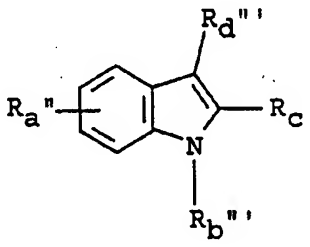


, (III)

in which
R_c is as defined in Claims 1 through 4,
R_a', R_b" and R_d" have the meanings given in Claims 1 through 4 for R_a, R_b and R_d with the condition that at least one of the radicals R_a, R_b and R_d contains a group convertible into a carboxyl group by hydrolysis, treatment with an acid or base, thermolysis or hydrogenolysis and/or R_b or R_d contains a group convertible into an NH_2-C9=NH) group by hydrolysis, treatment with an acid or base, thermolysis or hydrogenolysis,

is converted by means of hydrolysis, treatment with an acid or base, thermolysis or hydrogenolysis into a compound of general formula I, in which at least one of the radicals R_a, R_b and R_d contains a carboxy group and/or R_b or R_d contains an NH_2-C(=NH) group, or

c. To produce a compound of general formula I, in which at least one of the radicals R_a, R_b and R_d contains a group mentioned in Claims 1 through 4 convertible *in vivo* into a carboxy group, a compound of the general formula



, (IV)

in which
R_c is as defined in Claims 1 through 4,
R_a", R_b" and R_d" have the meanings given in Claims 1 through 4 for R_a, R_b and R_d, with the condition that at least one of the radicals R_a, R_b and R_d contains a carboxy group or a group convertible by means of an alcohol into *an appropriate* ester group,

is reacted with an alcohol of the general formula

$$HO - R_{10} \quad , (V)$$

in which
R_{10} is the alkyl part of one of the *in vivo* cleavable radicals mentioned in Claims 1 through 4 with the exception of the R_7-CO-O(R_8CR_9) group for a carboxyl group,

or with its formamide acetals

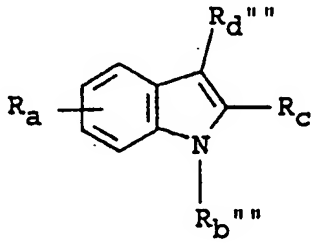
or with a compound of the general formula

$$Z_2 - R_{11} \quad , (VI)$$

in which

R_{11} is the alkyl part of one of the *in vivo* cleavable radicals mentioned in Claims 1 through 4 for a carboxyl group and
Z_2 is a starting group, or

d. To produce a compound of general formula I, in which R_2 is an in-vivo cleavable radical, a compound of the general formula



, (VII)

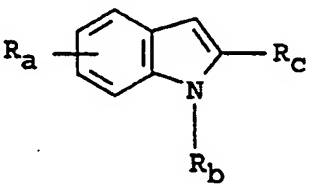
in which
R_a and R_c are as defined in Claims 1 through 4,
R_b" " and R_d" " have the meanings given in Claims 1 through 4 for R_b and R_d, with the condition that R_2 is a phenyl group substituted by an NH_2-C(=NH) group,

is reacted with a compound of the general formula

$$Z_3 - R_{12} \quad , (VIII)$$

in which
R_{12} is one of the in-vivo cleavable radicals mentioned in Claims 1 through 4 in the definition of the radical R_2 and
Z_3 means a nucleofugic starting group, or

e. To produce a compound of general formula I in which the R_2-A group is in the 3 position, R_2 is a cyanophenyl group and A is an n-C_{1-3}-alkylene group in which an indole-ring linked methylene group of the n-C_{1-3}-alkylene group is replaced by a carbonyl group, a -$COCH_2O$ or a -$COCH_2CH_2O$ group, the oxygen atom being linked to the radical R_2 in each case, a compound of general the formula



, (IX)

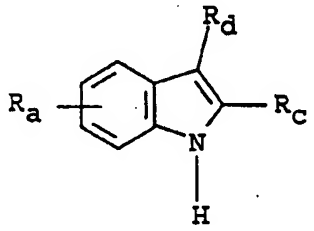
in which
R_a through R_c are as defined in Claims 1 through 4,

is reacted with a compound of the general formula

$$Z_4 - CO\text{-}A' - R_2' \quad , (X)$$

in which
R_2' means a cyanophenyl group,
A' means an n-C_{2-3}-alkylene group, a -CH_2O group or a -CH_2CH_2O group, the oxygen atom being linked to the radical R_2' in each case, and
Z_4 means a nucleofugic starting group, or

f. To produce a compound of general formula I in which the R_2-A group is in the 1 position and A is an n-C_{1-3}-alkylene group in which an indole-ring linked methylene group of the n-C_{1-3}-alkylene group is replaced by a carbonyl group, a -$COCH_2O$ group or a -$COCH_2CH_2O$ group, the oxygen atom being linked to the radical R_2 in each case, a compound of the general formula



, (XI)

in which
R_a, R_c and R_d are as defined in Claims 1 through 4,

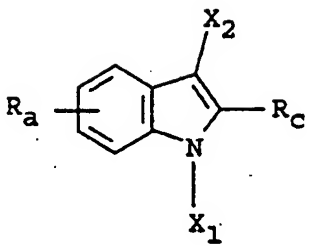
is reacted with a compound of the general formula

HO-CO-A'-R_2" , (XII)

in which
R_2" has the meanings given in Claims 1 through 4 for R_2 with the condition that R_1 is as defined in Claims 1 through 4 except for the hydrogen atom or is a protective radical for an amidino group and
A' is an n-C_{2-3}-alkylene group, a -CH_2O group or a -CH_2CH_2O group, the oxygen atom being linked to the radical R_2' in each case, or with reactive derivatives thereof,

optionally followed by cleavage of any protective radical used, or

g. To produce a compound of general formula I in which the R_2-A group is in the 1 or 3 position, R_2 is a cyanophenyl group and A is a -CONH group, a -CH_2CONH group, a -CH_2CH_2CONH group, a -$CONHCH_2$ group or a -$CONHCH_2CH2$ group, a compound of the general formula



, (XIII)

in which
R_a and R_c are as defined in Claims 1 through 4,
one of the radicals X_1 or X_2 is a C_{1-3}-alkyl group that can be substituted by a C_{1-3}-alkoxycarbonyl group, and the other radical X_1 or X_2 is an $HOOC-(CH_2)_n$ group in which

n is the number 0, 1 or 2,

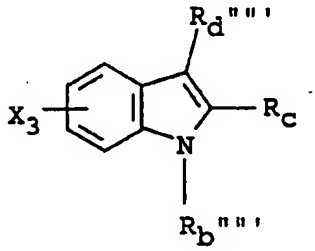
is reacted with a compound of the general formula

$$H_2N-(CH_2)_m-R_2' \quad , (XIV)$$

in which
R_2' means a cyanophenyl group and
m is the number 0, 1 or 2,

or with reactive derivatives thereof, or

h. To produce a compound of general formula I in which R_a is a C_{1-3}-alkoxycarbonyl group, an R_3R_4N-CO group, an $R_3R_4N-SO_2$ group or an R_4R_5N group and R_2 is a cyanophenyl group, a compound of the general formula



, (XV)

is reacted with a compound of the general formula

$$X_4-Y \quad , (XVI)$$

in which
R_c is as defined in Claims 1 through 4,
one of the radicals R_b""' or R_d""' is a C_{1-3}-alkyl group that can be substituted by a C_{1-3}-alkoxycarbonyl group, and the other of the radicals R_b""' or R_d""' is an R_2'-A group in which

A is as defined in Claims 1 through 4 and R_2' is a cyanophenyl group,

X_3 is an HO-CO or HO-SO_2 group, X_4 is a hydrogen atom and Y is a C_{1-3}-alkyl group or an R_3R_4N group or

X_3 is an R_4NH group, X_4 is a phenylamino, naphthylamino or R_6 group, with R_3 and R_4 being as defined in Claims 1 through 4, and R_6 having the meanings given in Claims 1 through 4 for R_3 except for the hydrogen atom, and

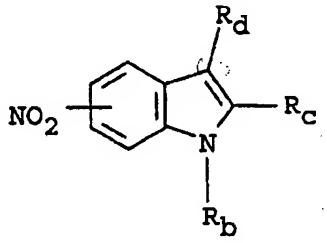
Y is an HO-CO or HO-SO_2 group, with the hydroxy group of the HO-CO or HO-SO_2 group together with the hydrogen atom of an amino group of radical X_4 also being able to be another carbon-nitrogen bond,

or with reactive derivatives thereof, and

if neccessary, a compound of general formula I thus obtained containing a reactive carboxyl function, is then converted with an appropriate aminoacid derivative into the desired compound of general formula I,

or, if necessary, a compound of general formula I thus obtained containing a reactive sulfonamide hydrogen atom, is converted with an appropriate halogen carboxylic acid derivative into the desired compound of general formula, or

i. To produce a compound of general formula I in which R_a is an amino group, a compound of the general formula



, (XVII)

in which
R_b through R_d are as defined in Claims 1 through 4 is reduced and

if desired, a compound of formula I thus obtained containing a pyridinyl nitrogen atom is then quarternized by means of alkylation at the pyridine nitrogen atom, and/or

a compound of formula I thus obtained containing an aromatically bound halogen atom is converted by means of dehalogenation into an appropriate compound, and/or

a protective radical used during the reactions to protect reactive groups is split off, and/or

a compound of general formula I thus obtained is separated into its stereoisomers, and/or

a compound of general formula I thus obtained is converted into its salts and, especially for pharmaceutical application, into its physiologically compatible salts with an organic or inorganic acid or base.